Clinical Utilisation of Respiratory Elastance in Clinical Environments

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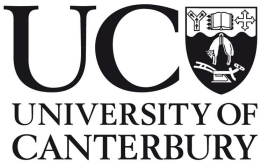

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Abstract

Mechanical ventilation (MV) is used to support or fully control patient breathing to treat respiratory failure. Patients with respiratory failure, specifically acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), require MV to fully control their breathing and provide adequate positive end-expiratory pressure (PEEP) to prevent alveolar lung collapse. ARDS patient have high mortality rates up to 60%, with significantly increased daily medical cost. Current practice in using MV to treat respiratory failure is a mixture of clinician intuition and generalised one size fits all approaches, which can lead to poor MV therapy care and ventilator-induced lung injury (VILI), increasing time on MV and cost, while reducing patient outcomes.

Currently, there are growing trends towards individualising care in medicine. In ventilation care, model-based methods are applied to identify patient physiology and respiratory mechanics to assist and guide ventilation therapy. Model-based methods can be utilised to provide greater insight to patient condition and allow more optimal patient-specific care. Optimal, personalised care would increase the quality of MV therapy and decrease the duration of MV. It would also reduce VILI and, as a result, decrease mortality and morbidity along with their associated costs.

Spontaneous breathing (SB) effort is when patients try to breath on top of the supported

MV breathe. SB patients are generally transitioned into assisted spontaneous breathing (ASB) ventilation modes, which synchronises with patient breathing and supports breaths based on their demand, resulting in reduced overall work of breathing and increased pulmonary gas exchange. However, SB breaths hinder the accuracy of identified patient-specific elastance. SB efforts can be highly variable and are not measurable without invasive tests, but would be clinically useful to know. In this thesis, SB is quantified utilising dynamic lung elastance $Edrs$. The time-varying elastance is the sum of alveoli elastance, chest wall elastance and patient elastance generated by the patient demand, and can be utilised to identify SB effort. The $Edrs$ trajectory is used by itself and again with proven basis function models to quantify patient demand and SB effort. The SB effort is identified and validated using measured electrical activity of the diaphragm (Eadi).

Preterm neonates are prone to respiratory failure syndrome (RDS) due to their prematurity, which sees reductions in alveoli growth and surfactant production. Thus, they require MV therapy to assist breathing due to their lack of respiratory development. Neonatal MV is common in the neonatal intensive care unit (NICU) and aims to minimise duration of MV as prolonged ventilation can lead to bronchopulmonary dysplasia or VILI.

Infants are known to exhibit different pulmonary mechanics compared to adults, and are also not widely studied. In this thesis, a first in-depth study on neonatal elastance is presented. The well-validated single compartment model of pulmonary mechanics is used to identify patient-specific elastance in this cohort, which consists of 535,428 breaths over N=10 patients. The model fit was good and was further validated by comparing with known physiological differences, such as weight, and use of surfactant.

Anecdotally, male infants are harder to ventilate than female infants. The sex differ-

ences between male and female infants stems from their fetal growth stage where, female infants are typically more developed than males by 1.5-2 weeks. This thesis quantifies sex differences in neonatal elatances and breath-to-breath variability of each cohort, a first of its kind result in MV for any cohort. Male infants shown higher specific elastance than female infants and thus have lower variability. The results indicate the potential for potentially entirely different approaches to MV care for male and female pre-term infants.

This thesis presents analyses of lung physiology, pulmonary mechanics, and quantification of SB efforts. These outcomes advances the state of the art in modelling and MV, particularly with first of its kind, in-depth analyses and results in NICU MV. The physiology and respiratory mechanics was successfully quantified in this cohort and further validated in sub-cohort analyses. These results presented would provide good basis for further clinical use of model-based methods in both adult and infant cohorts.

Publications

Over the course of this research, a number of papers have been published. The research demonstrated in these papers is based on the work presented in this thesis.

Journal Papers

- **Kim, KT**, Knopp, J, Dixon, B, Chase, JG (2019). ”Quantifying neonatal pulmonary mechanics in mechanical ventilation.” *Biomedical Signal Processing and Control*.

- **Kim, KT**, Knopp, J, Dixon, B, Chase, JG (2019). ”Mechanically ventilated premature babies have sex differences in specific elastance: A pilot study” *Pediatric Pulmonology*

- **Kim, KT**, Morton, S, Howe, S, Chiew, YS, Knopp, J, Docherty, P, Pretty, C, Desaive, T, Benyo, Balazs, Szlavecz, A, Moeller, K, Shaw, G, Chase, JG (2019). ”Model-based PEEP titration versus standard practice in mechanical ventilation: a randomised controlled trial” *Trials*

- Howe, SL, Chase, JG, Redmond, DP, Morton, SE, **Kim, KT**, Pretty, C, Shaw, GM, Tawhai, MH, Desaive, T (2019). ”Inspiratory respiratory mechanics estimation by using ex-

piratory data for reverse-triggered breathing cycles" *Computer Methods and Programs in Biomedicine*

Conference Papers

- **Kim, KT**, Redmond, D, Morton, S, Howe, S, Chiew, YS, Chase, JG (2017). "Quantifying patient effort in spontaneously breathing patient using negative component of dynamic Elastance" *20th IFAC World Congress 2017*, Toulouse, France 9-14 July 2017

- **Kim, KT**, Howe, S, Chiew, YS, Knopp, J, Chase, JG (2018). "Lung Mechanics in Premature infants: Modelling and clinical validation" *10th IFAC Symposium on Biological and Medical Systems (BMS) 2018*, Sau Paulo, Brazil 3-5 September 2018

- **Kim, KT**, Knopp, J, Dixon, B, Chase, JG (2020). "Comparison between single compartment model and recruitment basis function model on NICU patients" *IFAC-V World Congress 2020*, Germany July 11-17 2020.

- **Kim, KT**, Knopp, J, Dixon, B, Chase, JG (2020). "Physiological sex differences in mechanically ventilated premature neonates: A pilot study" *IFAC-V World Congress 2020*, Germany July 11-17 2020.

- Redmond, D, **Kim, KT**, Morton, S, Chiew, YS, Chase, JG (2017). "A Variable Resistance Respiratory Mechanics Model" *20th IFAC World Congress 2017*, Toulouse, France 9-14 July 2017

- Chakson, J, McNearney, E, Argus, F, Sutherland, C, Knopp, J, Redmond, D, **Kim, KT**, Chase, JG (2017). "Analysis of Neonatal Pulmonary Mechanics" *20th IFAC World Congress 2017*, Toulouse, France 9-14 July 2017

- Argus, F, Chakson, J, McNearney, E, Sutherland, C, Knopp, J, Redmond, D, **Kim, KT**, Chase, JG (2017). ”Predicting the Effects of Changing PEEP Using a Basis Function Method” *20th IFAC World Congress 2017*, Toulouse, France 9-14 July 2017

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system and the difficulty of starting up a clinical trial. Working with you on CURE was pleasurable and fascinating experience. Geoff, I sincerely hope CURE RCT would start in near foreseeable future.

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List of Abbreviations

ICU intensive care unit

LoMV length of mechanical ventilation

MV mechanical ventilation

NAVA neurally adjusted ventilatory assist

NICU neonatal intensive care unit

PS pressure support

SB spontaneous breathing

VFD ventilator free days

Technical Abbreviations

ALI Acute Lung Injury

ARDS Acute Respiratory Distress Syndrome

Eadi Electrical activity of the diaphragm

ETT endotracheal tube

PEEP positive end-expiratory pressure

P/F ratio PaO_2/FiO_2 ratio

RDS respiratory distress syndrome

VILI ventilator-induced lung injury

V/Q ratio V/Q ratio

CHAPTER 1

Introduction

1.1 Introduction

Mechanical ventilation (MV) is required for patients with respiratory failure (Sundaresan and Chase, 2012; Girard and Bernard, 2007; Major et al., 2018; Slutsky, 1999; Rose, 2010; Fan et al., 2018; Flaatten, 2013; Borges et al., 2006; Bos et al., 2018) and in particular, patients with a more severe form of respiratory failure, Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS). MV is an irreplaceable life support during the course of treatment and recovery (Sundaresan and Chase, 2012; Girard and Bernard, 2007; Major et al., 2018; Slutsky, 1999; Rose, 2010; Fan et al., 2018; Flaatten, 2013; Villar et al., 2013; Borges et al., 2006; Bos et al., 2018). Positive end-expiratory pressure (PEEP) and tidal volume are the key ventilator parameters when treating ARDS and other forms of respiratory failure (Villar et al., 2006; Girard and Bernard, 2007; Brower et al., 2000; Amato et al., 1998; Meade et al., 2008; Mercat et al., 2008a; Oba et al., 2009; Briel et al., 2010; Bos et al., 2018; Hickling et al., 1990). Equally, the use of low tidal volume settings results in lower mortality rates (Villar et al., 2006; Brower et al., 2000; Bos et al., 2018;

Amato et al., 1998; Hodgson et al., 2011; Hickling et al., 1990). It has also been proposed that setting PEEP to where the lung had minimum elastance would be clinically beneficial (Suarez-Sipmann et al., 2007; Carvalho et al., 2013a, 2007; Sundaresan et al., 2009; Chiew et al., 2012) as, at this point, the lung has the largest volume for the least pressure input, which minimises risk of overstretching the lung tissue and creating further damage.

The current practice in treating respiratory failure is based on either clinician intuition or a generalised, "one size fits all" approaches (Fan et al., 2017; Amerling et al., 2008; Fernandez et al., 2015). Poor treatment increases the risk of ventilator-induced lung injury (VILI) through poor choices in settings that either overdistend the lung or provide too little support to maintain lung recruitment (Brochard et al., 2017; Fan et al., 2008; Pannu and Mehta, 2004; Parker et al., 1993; Gattinoni et al., 2003; Dreyfuss and Saumon, 1998; Slutsky and Ranieri, 2013a). The main outcomes of sub-optimal MV care are increased risk of morbidity and mortality, especially in patients with ARDS. ARDS patients already have mortality rates up to 60% and significantly increased medical cost per day (Dasta et al., 2005; Phua et al., 2009). Therefore, any methods to improve care and shorten the length of mechanical ventilation (LoMV) would significantly impact outcomes and economic cost.

In addition, there are growing trends towards individualising care in medicine. However, in ventilation care, there has not been a significant study based employing personalised or patient-specific care (Chase et al., 2018). Tools such as ventilators, computers, and other technology can measure, identify and perform care more precisely and efficiently and yet the fundamental modes of treatment have not significantly changed in the last 30 years.

Premature infants are one cohort which is highly susceptible to respiratory distress syn-

drome (RDS), due to their prematurity at birth and thus have under-developed lungs (Brown and DiBlasi, 2011; Liggins et al., 1972; Carroll and Agarwal, 2010; Jobe and Ikegami, 1998; Kotecha, 2000; Polin et al., 2014). Premature infants lack surfactant production in their lungs to prevent lung collapse (atelectasis) and maintain alveoli recruitment (Jobe and Ikegami, 1998; Brown and DiBlasi, 2011; Thomas, 1971; Goerke, 1998; Wood and Jobe, 1993). Therefore, MV is vital tool used to treat RDS or othFer respiratory failure. According to O'Donnell et al. (2004), 3-5% of newborn infants worldwide require resuscitation at birth each year. This statistic makes it one of most frequently performed aspects of care in the neonatal intensive care unit (NICU). There are various guidelines (Sweet et al., 2010; Niermeyer et al., 2000; Kattwinkel et al., 1999) on how these procedures should be performed, but while they agree adequate ventilation is the key to successful resuscitation, there is little agreement on the implementation of MV.

Utilising a model-based method can achieve greater understanding of the patient condition and allow better clinical judgement (Chase et al., 2011, 2018). Simple models allow low computational requirement and can thus easily be applied clinical environment and utilised in real-time to support clinicians by providing greater insight on patient-specific underlying condition. Such tools would lead to much more personalised, patient-specific care to reduce both length of mechanical ventilation and VILI, and as result, mortality, cost and time.

1.2 Lungs

The major role of the lungs is to process gas exchange between oxygen, O_2, and carbon dioxide, CO_2. Gas exchange occurs between the lung alveolar air and blood of pulmonary capillaries (Neumann and Von Ungern-Sternberg, 2014; West, 1975). The flow of air into and out of the alveoli is ventilation (V) and the flow of blood to capillaries is perfusion (Q). During inspiration, fresh oxygen is delivered to alveoli and during expiration carbon dioxide is emitted. Clinically, it is common to measure the ratio of ventila-

tion and perfusion to determine patient's gas exchange, where a low V/Q ratio can lead to hypoxemia (low oxygen level in the blood).

Although the major function of the lungs are to deliver gas exchange, lungs are controlled by diaphragm. Diaphragm is a muscle that is located under the base of chest and separates between chest and abdomen. During inspiration, the diaphragm contracts and flattens creating a vacuum effect and pulls the air into the lungs through trachea bifurcating into bronchus which branches into bronchioles and finally, into alveoli sacs. The diaphragm relaxes during expiration and thus air is pushed out of the lungs. The basic physiology of lung can be seen Figure 1.1

Gas exchange in the alveoli occurs primarily through diffusion. Oxygen travels from the alveoli to capillary blood through alveolar surfactant,the alveolar epithelium, the basement membrane, and the capillary endothelium (Goerke, 1998; Neumann and Von Ungern-Sternberg, 2014; West, 1975). Alveolar surfactant or pulmonary surfactant is a lipoprotein and lowers the surface tension the lungs and thus, prevents atelectasis (Goerke, 1998; Neumann and Von Ungern-Sternberg, 2014; West, 1975).

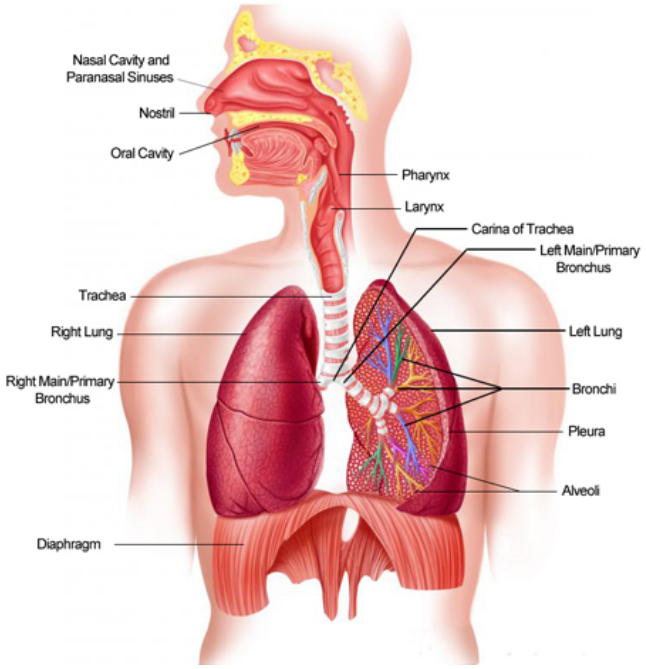

Figure 1.1: Lung physiology structure. Image from FIRST AID for free!. Url: `https://www.firstaidforfree.com/how-do-we-breath-a-guide-to-the-respiratory-system/`

1.3 Mechanical Ventilation

Mechanical ventilation (MV) is used to treat respiratory failure. A ventilator either fully controls or partially supports patient breathing with the goal of enduring efficient gas exchange. This approach reduces the work of breathing done by the patient and allows time for recovery. For patients with respiratory diseases like ARDS, it also prevents lung collapse, also known as atelectasis (Pelosi et al., 2001; Halter et al., 2003). There has been a great deal of research on setting optimal MV parameters, from which there is consensus on the use of low tidal volumes as it has been shown to reduce mortality and increase ventilator free days (VFD) (Brower et al., 2000; Girard and Bernard, 2007). However, on other MV settings and parameters, there have only been conflicting results (Amato et al., 1998; Villar et al., 2006; Meade et al., 2008; Briel et al., 2010), as reviewed by Major et al (Major et al., 2018)

PEEP is known to reduce hypoxemia and intrapulmonary shunting in ARDS patients

and the clinical practice of titrating PEEP ameliorates these effects (Mercat et al., 2008a). PEEP-induced alveolar recruitment helps to avoid airway collapse and reopening, protects lung surfactant and improves ventilation homogeneity within the lung (Mercat et al., 2008a). Although alveolar recruitment and oxygenation are often related, oxygenation is complex and affected by many factors and therefore should not be used as a surrogate for recruitment (Mercat et al., 2008a).

Throughout the duration of MV therapy, patient condition will start to improve and lower level of sedations will be used. Thus, patient will attempt to breathe by themselves on top of supported MV breathe. This natural breathing performed by the patient is called spontaneous breathing effort (SB). SB introduces both patient-ventilator asynchrony and can lead to poor ventilation outcomes (Epstein, 2011; Chiew et al., 2018; Freebairn and Hickling, 2005; Hickling et al., 1990; Major et al., 2018). Therefore SB patient would undergo assisted spontaneous breathing modes (ASB), which are designed to support patients natural breathing. These modes are typically used as intermediate steps before weaning the patients of MV.

ASB modes aim to reduce work of breathing done by the patient by synchronising with patient breathing patterns while providing adequate pressure and oxygen. The amount of pressure and oxygen are typically determined by patient-specific demand triggers. ASB modes have been known to increase pulmonary gas exchange, systemic blood flow, and oxygen supply to the tissue (Burchardi, 2004; Putensen et al., 2005; Spahija et al., 2010; Brander and Slutsky, 2006; Freebairn and Hickling, 2005; MacIntyre, 1986).

Improved patient condition during ASB will lead to weaning the patient off MV and from endotracheal tube (ETT) (Boles et al., 2007). This process is important and efficient weaning process is desired as it reduces length of mechanical ventilation (LoMV). Reducing LoMV through both efficient MV strategy and weaning will lead to lower chance

of VILI, reduce significant costs associated with MV, and most importantly improved patient care.

Mechanical Ventilation for preterm neonates is one of most commonly practiced forms of MV care around the world (Sweet et al., 2013, 2010; Brown and DiBlasi, 2011). Treating respiratory failures of preterm neonates require invasive MV. The risks of invasive MV on infants is they are susceptible to inflammation and lung injury caused by the ventilator. One cause of this injury is the lack of understanding of the physiological differences between adult lungs and preterm neonate lungs.

Patient ventilator asynchrony or dyssynchrony can occur when MV is mis-matched with patient breathing efforts. Asynchrony is common in the ICU occurring up to 25% ventilated patients (Mellott et al., 2014). Asynchrony may occur due to low sedation level or poor ventilator settings, or ineffective triggering. In neonates, it may also occur when infant is crying or coughing. Asynchrony in adults is known to be associated with significant patient discomfort, poor gas exchange, VILI, prolonged ventilation and higher mortality (Thille et al., 2006; Chao et al., 1997; Epstein, 2011; Mellott et al., 2014). However, asynchrony in unstudied in neonates, but it is reasonable to assume a similar overall negative impact.

1.4 MV in Adults

1.4.1 ARDS/ALI

The Berlin definition of ARDS is defined as a ratio of partial arterial oxygen pressure and fractional inspired oxygen (PaO2/FiO2) less than 300mmHg (Flaatten, 2013; Ranieri et al., 2012). The causes for ARDS are non-cardiogenic pulmonary edema, decreased pulmonary compliance, and ventilation perfusion mismatch (Dunkel, 2006; Raghavendran and Napolitano, 2011). The core treatment for ARDS is MV (Sundaresan and Chase,

2012; Mertens et al., 2009; Brower et al., 2000, 2001; Brochard et al., 1998). MV is an irreplaceable form of life support during the course of treatment and recovery (Brower et al., 2001). To treat ARDS/ALI, high doses of oxygen and PEEP are used to maximise the recruitment of collapsed alveolar (Hodgson et al., 2011; Oczenski et al., 2004; Riva et al., 2009). MV assists breathing by either completely or partially taking over the patient's breathing effort (Ducharme-Crevier et al., 2015; Oliva et al., 2012). In doing so, it provides the support required to allow the patient's lung to recover.

Severe forms of respiratory failure, such as ARDS, occur due to inflammatory response in the lung. This inflammation, due to disease or trauma, impairs patient breathing efforts as alveoli collapse, which significantly reduces gas exchange. This loss of gas exchange is the main course of the resulting high, mortality and morbidity rates in ARDS. The mortality rate from ALI or ARDS is approximately 40 to 50% (Bersten et al., 2002; Sigurdsson et al., 2013). The variability in reported numbers is largely due to the variability in quality and care resulting from lack of a consensus approach to MV in these patients and in general.

More specifically, Patients with ALI/ARDS develop pulmonary edema, resulting in clinically stiff, non-compliant, and heterogeneous lungs with regards to healthy alveoli and alveoli that are inflamed and filled with fluid, and others that are unscathed. For this reason, excessive pressure or tidal volumes to increase recruitment of injured alveoli can cause additional lung damage and may result in VILI (Villar et al., 2006; Lipes et al., 2012). VILI is difficult to diagnose as it overlaps with, or is secondary to, the actual disease being treated, but its presence leads to longer, more difficult recovery and/or increased mortality. Hence, setting pressure, in particular, is a careful patient-specific balance, which is often overlooked in protocolised "one size fits all" approaches (Major et al., 2018; Chase et al., 2018).

The use of low tidal volumes and a plateau pressure of less than $30 cm H_2O$ have been reported to decrease mortality and morbidity amongst patient with ARDS (Brower et al., 2000). According to The Acute Respiratory Distress Syndrome Network, a RCT was conducted to compare the difference between treatment with lower tidal volume and traditional tidal volume. The traditional tidal volume was 12ml per kilogram of predicted body weight and lower tidal volume was 6ml per kg of predicted body weight. The study showed the mortality rate of patients treated with lower tidal volume was lower, and also increased number of ventilator free days (Brower et al., 2000; Lipes et al., 2012). It has also been found lower tidal volumes, or a lung protective ventilation strategy, reduces VILI (Neto et al., 2014). Equally, Amato et al. (2015) showed minimum driving pressures per unit recruited volume improved outcomes. However, all these results provide only basic guidance within which care is still highly variable and inefficient (Carvalho et al., 2007; Sundaresan et al., 2009; Chiew et al., 2012).

There are many generalised approaches for guiding MV therapy. For example, the ARDSNet, EXPRESS, and ALVEOLI study protocols (Brower et al., 2000, 2004; Meade et al., 2008; Mercat et al., 2008a; Briel et al., 2010). However, these approaches are built on population studies and cannot capture the heterogeneity and patient-specificity of ALI/ARDS. Currently, there are no conclusive, generalisable approaches or methods for PEEP selection Sundaresan and Chase (2012); Major et al. (2018).

PEEP is important parameter setting and it has been proposed to be set at minimal elastance (Carvalho et al., 2007; Suarez-Sipmann et al., 2007; Lambermont et al., 2008; Chiew et al., 2011; Pintado et al., 2013; Chiew et al., 2015a; Amato et al., 2015). The goal is to balance the risks of low PEEP, causing repeated collapse and recruitment (atelectrauma), or high PEEP, causing overdistension, both of which lead to VILI. Minimum elastance provides, by definition, the maximum recruitment for minimum pressure, thus balancing rewards and risk.

Experimental animal trials have induced ARDS in pigs and reported had minimal respiratory elastance at a specific PEEP was associated with higher oxygenation, maximum recruitment, and higher functional residual capacity, without evidence of VILI (Carvalho et al., 2007). Experimental human studies suggest setting PEEP to minimal respiratory elastance or maximum compliance, where elastance is the inverse of compliance, may be beneficial (Suarez-Sipmann et al., 2007; Amato et al., 2015). Despite these findings, the current standard of care does not utilise this data, as it is hard to accurately estimate elastance in real-time. Instead, typical care reverts to clinical intuition or a generalised approach lacking patient-specificity and thus unable to accurately address the significant inter- and intra- patient variability these patients exhibit..

Model-based mechanical ventilation is desired as it provides more detailed patient-specific data which can be used to reduce the length of mechanical ventilation (LoMV) (Major et al., 2018; Major, 2015). Minimal elastance PEEP selection is one of a few new methods proposed for MV therapy for patients with ALI/ARDS (Suarez-Sipmann et al., 2007; Amato et al., 2015) and is much more feasible using model-based methods (Chase et al., 2018; Morton et al., 2018, 2019b,a). At the University of Canterbury and the Christchurch Hospital intensive care unit (ICU), research has been performed to use a model-based method to create model-based ventilation therapy (Chiew et al., 2011; Redmond et al., 2014; Chiew et al., 2015a; Chase et al., 2018; Morton et al., 2019b,a). This model uses model identified patient specific and breath-specific respiratory mechanics that provide greater insight in treating ALI/ARDS than pressure and flow curves alone. Pilot studies have been conducted and have shown great potential (Chiew et al., 2011, 2015c). A randomised control trial (RCT) is currently under way to show the effectiveness of this model-based treatment over current clinical practice (Szlavecz et al., 2014; Kim et al., 2020).

A Randomised Controlled Trial (RCT) is a medical experiment to show effectiveness of

a treatment. It is often used in medical community as it is proof a new treatment is superior over the current treatment approach (Hariton and Locascio, 2018; Altman, 1981; Akobeng, 2005; Sibbald and Roland, 1998; Calvert et al., 2018). Generally RCTs are conducted whereby a patient eligible for the trial is randomly selected into either a control or intervention group. The randomisation itself removes any bias towards one treatment over the other, as patients are selected and matched between cohorts based on diagnosis and age. Depending on the trial, participants may be blinded (group allocation is concealed until end of study) to remove bias when conducting the experiment (Karanicolas et al., 2010). In the medical field, a well blinded study is considered a gold standard and is commonly used to test efficacy of new form of intervention.

1.4.2 Clinical Utilisation of Respiratory Elastance (CURE) Trial

The Clinical Utilisation of Respiratory Elastance (CURE) is ongoing RCT designed by researchers at University of Canterbury and Christchurch Hospital ICU (Chiew et al., 2015c; Kim et al., 2020). Given the diversity of lung condition in patients with respiratory failure, the inter-variability between patients can be significant along with time-varying intra-patient variability. Hence, a patient specific and time specific or evolving treatment approach is desired. For this reason, a model-based PEEP selection method has been developed (Chiew et al., 2011, 2015a). This model-based and patient specific approach offers the ability to identify and directly manage intra- and inter- patient variability in response to care, and thus has the potential to guide MV therapy based on a patient-specific condition and real time-response to care. This procedure has been clinically validated in pilot trials at Christchurch Hospital ICU (Chiew et al., 2015c).

The CURE RCT is a single centre trial, conducted at the Christchurch Hospital ICU, New Zealand. This trial aims to recruit 320 patients, 160 in intervention and 160 in control group, where intervention will utilise model-based method with protocolised recruitment manoeuvres and PEEP will be selected to minimal elastance afterwards (Kim et al.,

2020; Chiew et al., 2015c; Major, 2015; Major et al., 2018). The control group will be current standard practice. The aim of this RCT is to utilise model-based methods to reduce LoMV (the length of MV), and improve patient care and outcomes.

1.5 MV in Preterm Neonates

1.5.1 Neonatal Lung and development

Prematurely born infants in the neonatal intensive care unit (NICU) have different lung mechanics compared to both adults or children. They severely lack in total numbers of alveoli and they also lack surfactant production (Neumann and Von Ungern-Sternberg, 2014; Brown and DiBlasi, 2011). The lack of alveoli and surfactant causes a reduction in collagen and elastin and thus a reduced functional residual capacity (FRC) in the lung (Neumann and Von Ungern-Sternberg, 2014; Brown and DiBlasi, 2011; Carroll and Agarwal, 2010). This reduction makes them more susceptible to VILI during MV therapy because the lung is actually much stiffer (Brown and DiBlasi, 2011; Carvalho et al., 2013b; Kannangara et al., 2018). Stiffer (non-compliant) lungs can lead to both VILI or longer duration of MV. For this reason, when invasive MV is used, strategies are now focused to reduce the time of invasive MV (Brown and DiBlasi, 2011; Jobe, 2009).

Lung development is an ongoing process starting as early as 26 days of gestational age (GA) as it grows during prenatal and postnatal phase. Lung development is highly variable between individuals, but can be divided into 5 distinct stepwise phases (Hislop et al., 1986; Colin et al., 2010; Copland and Post, 2004; Joshi and Kotecha, 2007; Carroll and Agarwal, 2010):

1. Embryonic Phase (26 days to 6 weeks GA)
2. pseudoglandular (6-16 weeks GA)
3. canalicular (16-28 weeks GA)

4. saccular (28-36 weeks GA)
5. alveolar (36 weeks GA to term)

Even after the alveolar growth phases, the lung continuously develops until childhood (Colin et al., 2010). The bronchial branching is developed by 16 weeks of GA. During the canalicular phase (16-28 weeks GA), the conducting airways and terminal bronchioles are formed. The saccular phase is when clusters of sacs are formed on the terminal bronchioles and alveoli are starting to form. During the alveolar phase, the alveoli matures and the two capillaries become single capillary, and lungs are able to carry out functioning gas exchange (Colin et al., 2010; Joshi and Kotecha, 2007). It is around 32 weeks of GA, alveoli begin to develop, and during alveolar phases, the alveoli grow in numbers and maturity. At term, infants have around 30% of the alveoli of an adult (Jobe, 2002).

As a result, the total lung volume significantly increases during the last trimester of gestation (saccular to alveolar to term) (Langston et al., 1984). Langston et al. (1984), states at 30 weeks of GA, the lung volume is only 34% of the lung volume at mature birth and at 34 weeks, the lung volume is at 47%. This rapid increase in lung volume occurs during the lung development as the air-space walls decrease in thickness and other development (Langston et al., 1984).

There is a hypothesis that preterm delivery, regardless of any neonatal respiratory disease, may have adverse effects on the lung growth and development. These adverse effects persist and worsen during the first 5 years of life (Stocks et al., 2007; Jobe, 2002; Hjalmarson and Sandberg, 2002; Greenough, 2007; Gappa et al., 2003).

1.5.2 Respiratory Distress Syndrome (RDS)

Respiratory distress syndrome (RDS) in infants is a condition of pulmonary insufficiency commencing at or after birth. Without treatment, it can lead to hypoxia and respiratory failure (Sweet et al., 2010; Lauterbach et al., 2001). The deficiency and immaturity of alveolar surfactant along with structural immaturity of the lung causes RDS. The treatment for RDS generally involves oxygen administration, positive pressure lung inflation, and surfactant replacement therapy (Brown and DiBlasi, 2011; Keszler, 2009; Sweet et al., 2010, 2013). The problem is these practices can vary depending on the gestation period the infant (O'Donnell et al., 2004; Brown and DiBlasi, 2011).

Surfactant is a lipoprotein which lowers the surface tension of the lungs to prevent atelectasis. Infants with RDS commonly undergo surfactant replacement therapies, as they have shown to reduce mortality and decrease the incidence of pneumothorax (air leak) (Griese, 1999; Polin et al., 2014; Sweet et al., 2013). Surfactant replacement therapies have been shown to increase lung function and are thus a reliable method to reduce length of mechanical ventilation (LoMV) (Yuksel et al., 1993; Wood and Jobe, 1993).

Preterm neonates have deficient surfactant. This lack of surfactant causes a reduction in collagen and elastin and thus a reduced functional residual capacity (FRC) in the lung (Brown and DiBlasi, 2011; Lista et al., 2017). This reduction makes them more susceptible to VILI in MV because the lung is much stiffer (Brown and DiBlasi, 2011; Carvalho et al., 2013b). It is thus problematic for treating preterm neonates with invasive MV. For this reason, when invasive MV is used, strategies are now focused on reducing the time of invasive MV (Brown and DiBlasi, 2011).

Overall, invasive ventilation of the neonate is effective, but can also lead to serious damage. Preterm neonates with respiratory failure require invasive ventilation, but

MV is known to be associated with VILI and bronchopulmonary dysplasia (BPD) (Carvalho et al., 2013b; Jobe and Bancalari, 2001; Kair et al., 2012). BPD occurs when the bronchi are damaged causing destruction of alveoli, and thus can be caused by either over-oxygenation or VILI (Kair et al., 2012; Jobe and Bancalari, 2001).

PEEP is significant parameter in neonatal ventilation, just as in the adult case, as it is the main determinant of FRC and thus available lung volume in intubated infants. The use of adequate PEEP also conserves surfactant and increases lung volume, surface area and compliance. Hence, as in adults, it is a critical parameter with little consensus on how to find or maintain an optimal PEEP level.

The use of low tidal volume to reduce lung injury has been shown in adults (Brower et al., 2000), but not in neonates. There is little clinical evidence using lower tidal volume reduces lung inflammation (Donn and Boon, 2009; Chow et al., 2002). According to (Brown and DiBlasi, 2011), 5ml/kg of tidal volume for preterm neonates resulted in improved outcomes in comparison to a 3ml/kg group. The 3ml/kg group had higher inflammatory response and a longer duration of MV. These unexpected results, compared to adults, may be explained by a comparison of adequate and inadequate tidal volume, rather than high and adequate tidal volume. Equally, they may indicate the neonatal lung is not simply a small adult lung.

High Frequency Oscillatory Ventilation (HFOV) is a specific ventilation mode delivering relatively very small tidal volumes at rapid rates superimposed on a variable mean airway pressure. There are studies suggesting that HFOV is more effective when ventilating preterm neonates (Gerstmann et al., 1996; Group, 1993; Yoder et al., 2000; Plavka et al., 1999). However, some reviews and RCTs have shown conflicting results in this area. One study by Courtney et al. (2002) concluded HFOV has small benefit in terms of the pulmonary outcome for very low birth weight infants, whereas Cools et al. (2010);

Van Reempts et al. (2003); Rettwitz-Volk et al. (1998); and Sweet et al. (2013) concluded there is no benefit in using HFOV on the basis of gestational age, birth weight and initial lung disease severity. Hence, as with the adult case, there is no consensus.

1.5.3 Sex Differences in boys and girls

Unlike adults, there is a wide range of literature comparing differences between male and female preterm neonates (Carey et al., 2007; Torday et al., 1981; Miller and Futrakul, 1968; Stevenson et al., 2000; Peacock et al., 2012). Preterm infants are born with varying gestational age and size. However, in utero, male foetuses are less developed than females at the same gestational age by 1.5 to 2 weeks (Torday et al., 1981). The newborn male infants also have higher incidence of RDS, morbidity, and mortality than females at the same birth weight (Torday et al., 1981; Miller and Futrakul, 1968; Stevenson et al., 2000). For these reasons, male infants are more likely to receive invasive MV (Stevenson et al., 2000). Anecdotally, it is known male infants are harder to ventilate, but no studies have yet quantified any differences in lung stiffness or mechanics to support this observation.

Male infants are less developed than females at the same birth weight or gestational age. Therefore, male infants lack surfactant production more than females (Torday and Nielsen, 1987). Deulofeut et al. (2007) showed females responded better to treatment and had lower length of stay. These anecdotes along with known differences in sex has yet to be quantified. It can be hypothesised males will have higher elastance compared to female infants based on the literature. However, no study has calculated any of the fundamental pulmonary mechanics of infants in NICU.

1.6 Preface

Mechanical ventilation in respiratory failure and pathology of ARDS, ALI, and RDS is discussed in this chapter. The importance of optimal MV parameters is discussed in

terms of minimising, both VILI and improving efficient gas exchange. Thus, reducing length of mechanical ventilation and improving overall MV therapy. This thesis covers twofold main sets of outcomes and Figure 1.2 shows how these outcomes are related:

1. First NICU analysis and unique data sets - variability, size, range of elastance, and on top of its sex differences, which in turn shows the model sensitive to important differences.
2. Second, how to deal with spontaneous breathing, prevalent in NICU MV, based on first analysis in a relatively unique adult cohort.

In adults, an approach is presented to quantify patient spontaneous breathing effort, which remains an important and unquantified clinical parameter, and protocol for a randomised control trial of model-based MV to be undertaken is presented. The quantification of SB effort performed in this thesis allows separation of active patient demand and passive patient-specific lung mechanics (elastance) without use of invasive or additional sensors. This metric can be further developed and utilised in clinical setting to give further information of on SB patients during ASB mode ventilation. It can also be used to adjust ventilator parameters to further reduce patient-specific work of breathing and speed up the weaning process, ultimately resulting in decreased LoMV.

The second part of this thesis aims to apply model-based methods to pre-term neonates. While model-based methods have been somewhat widely studied in adult cases, there has not been any in-depth study for pre-term neonates. Thus, this research presents a first ever extensive study on model-based methods in this cohort beginning with identifying and verifying physiology and respiratory mechanics parameters for this cohort for the first time. The single compartment model was utilised to identify patient-specific elastance in neonates and was also used to show significant differences in sex. Basis function modelling was also utilised in attempt to separate patient-specific SB effort

from passive pulmonary mechanics.

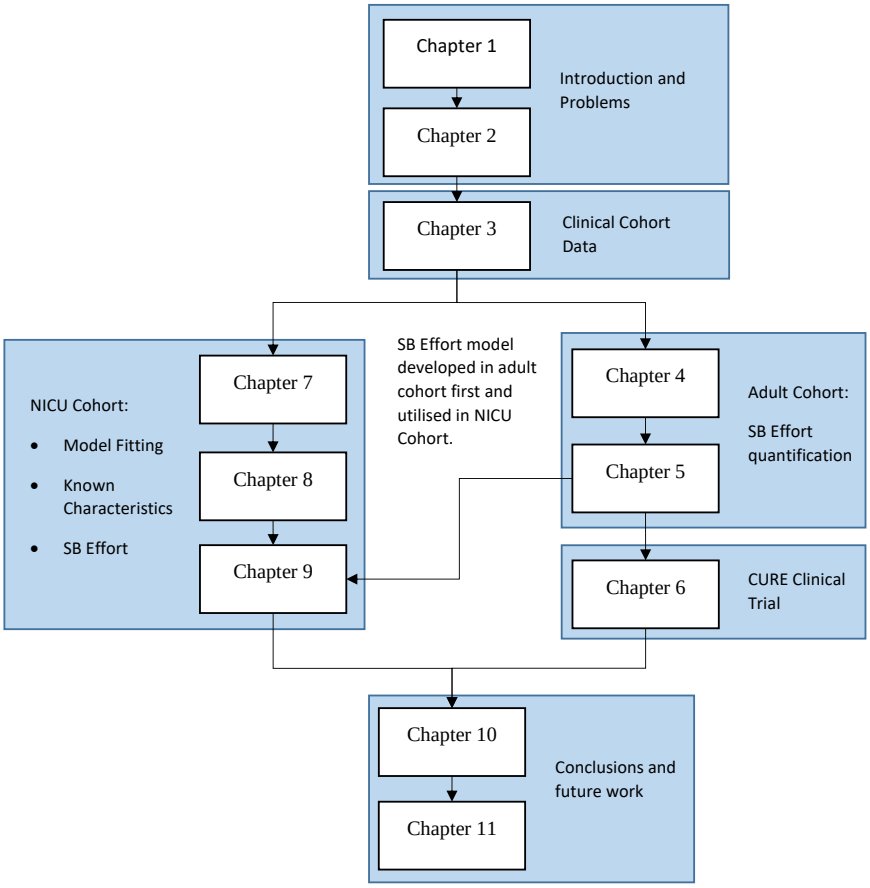

Figure 1.2: Thesis overview flowchart

Chapter 2 introduces the foundation models used in this thesis. It covers three major different models and presents the derivation of each of them and their physiological and mechanical relevance.

Chapter 3 presents the two, adult and neonatal cohorts, and associated data sets used in this thesis.

Chapter 4 develops an initial basis for quantifying patient-specific and breath-specific spontaneous breathing effort in adults using a time-varying elastance model. This approach aims to identify spontaneous breathing effort from inspiratory effort and is verified with known electrical activity of the diaphragm. This work has previously been

published in Kim et al. (2017).

Chapter 5 utilises validated basis function models with a time-varying elastance model to separate patient effort and patient respiratory mechanics, providing a potentially better estimate of this clinical parameter.

Chapter 6 presents protocol for CURE RCT. This clinical protocol explains the trial design for model-based MV in the adult intensive care unit, and includes all trial details and design. This work has previously been published in Kim et al. (2020).

Chapter 7 identifies patient-specific and breath-specific lung elastance using the validated single compartment model in neonatal cohort. Known physiological factors affecting elastance, such as surfactant and weight are used to further validate the results obtained. It is first-ever analysis of model-based and patient-specific lung mechanics in this cohort. This work has previously been published in Kim et al. (2019a).

Chapter 8 explores sex difference in lung mechanics, specifically the mass normalised in elastance, in neonates. The specific elastance accounts for weight and allows direct comparison between patients. Sex differences are sometimes explored in this neonatal cohort, but none have examined breathing mechanics in comparing male and female cohorts. This outcome differences found are validated against clinical reports and expectations and represent novel results in the field with potential clinical impact. This work has previously been published in Kim et al. (2019b).

Chapter 9 quantifies spontaneous breathing effort in neonatal cohort with similar approach as taken in Chapter 5. Neonates are not sedated during their ventilation period and thus quantifying patient-specific and breath-specific breathing effort in this cohort can provide further insight and clinical value.

Chapter 10 summarises the work performed and concludes this thesis, delineating main outcomes.

Chapter 11 provides plans and suggestions for potential future work.

CHAPTER 2

Equations and Models

2.1 Model-Based Mechanical Ventilation

The diversity of lung condition in patients with respiratory failure shows significant inter- and intra- patient variability. Thus, a patient specific and time specific or evolving treatment approach is desired. The ability to track and view patient's current lung condition will allow patient-specific care and thus, able to achieve more optimal ventilation therapy. Using model-based methods allow prediction of lung condition. Calculating for every breath allows further understanding of patients condition over time.

Model-based methods allow greater insight to patient condition by identifying patient-specific respiratory mechanics, which in turn can provide further insight into underlying patient condition (Chiew et al., 2015a; Greenspan et al., 1988; Schranz et al., 2013; Kim et al., 2019a; Morton et al., 2019b; Sundaresan et al., 2011; Sundaresan and Chase, 2012; Ben-Tal, 2006). A wide range of models have been successfully used in adult ICU patients to calculate patient-specific lung mechanics (Chiew et al., 2011, 2015a, 2018;

Schranz et al., 2013; Morton et al., 2019b,a; Howe et al., 2020). In particular, the single compartment model is the most basic model which represents as a single homogeneous volume with associated elastance (1/compliance) and airway resistance (Bates, 2009; Chiew et al., 2011; Kim et al., 2019a). A real-time implementation of this model allows real-time identification of lung mechanics at the patient bedside (Szlavecz et al., 2014; Chiew et al., 2011).

2.2 Single Compartment Model

The linear single compartment model also known as lumped parameter model has been commonly been utilised to estimate lung stiffness, also known as elastance (1/compliance) (Chiew et al., 2011; Sundaresan et al., 2011). This model treats the respiratory mechanics as a balloon connected to a pipe. The balloon is a reservoir (lung space) with elasticity modelled as a spring (elastance) (Bates, 2009). The pipe captures the endotracheal tube (ETT), and thus the flow resistance. Figure 2.1 shows diagram of the single compartment model.

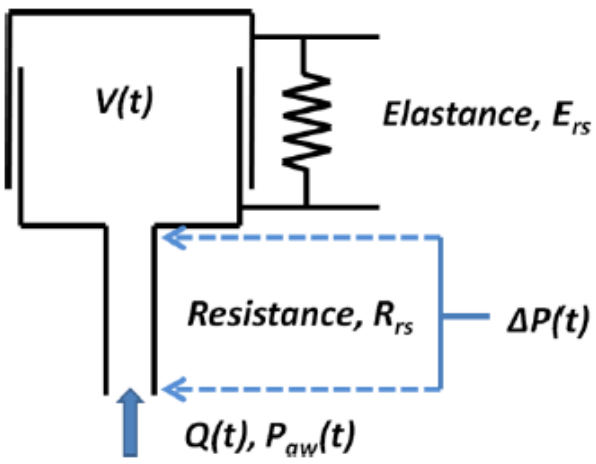

Figure 2.1: Single compartment model diagram, (Left) Mechanical definition, (Right) Electrical definition.

The tension of the spring or elastance in Figure 2.1, increases linearly as it is stretched. The pressure inside the lung also linearly increases with the volume. Thus, the pressure

inside the lung is defined:

$$P_{lung}(t) = E_{rs}V(t) \tag{2.1}$$

Flow of air is delivered to the lungs by MV via endotracheal tube (ETT) and thus, a driving pressure (ΔP) is required:

$$\Delta P(t) = R_{rs}Q(t) \tag{2.2}$$

Therefore the airway pressure is the sum of the pressure inside the lung from Eq 2.1 and pressure required to deliver oxygen Eq 2.2 and yields:

$$\begin{aligned} P_{aw} &= P_{lung} + \Delta P \\ P_{aw} &= E_{rs}V + R_{rs}Q + PEEP \end{aligned} \tag{2.3}$$

Where P_{aw} is the airway pressure, E_{rs} is respiratory elastance, V is the volume, R_{rs} is the airway resistance, Q is the air flow, and $PEEP$ is the offset pressure (or applied PEEP if there is no intrinsic PEEP). E_{rs} and R_{rs} are identified with least mean squared fit using $P_{aw}(t)$, $Q(t)$, and $V(t)$ as input parameters. The model is fit to inspiration for every breath (Chiew et al. 2011), where inspiration is positive gas exchange and therefore the period over which flow is positive. Expiration is the period during which flow is negative.

2.3 Basis Functions

Basis functions have been previously used in adult critical care models (Langdon et al., 2016, 2017; Morton et al., 2018, 2019b). In particular, Morton et al. (2019b) utilises basis functions to describe alveoli recruitment and distension (Morton et al., 2019b). The shape of basis functions for alveoli recruitment and distension are shown in Figure 2.2. Morton et al. (2019b) showed the model identifies distension at high PEEP (Morton et al., 2019b).

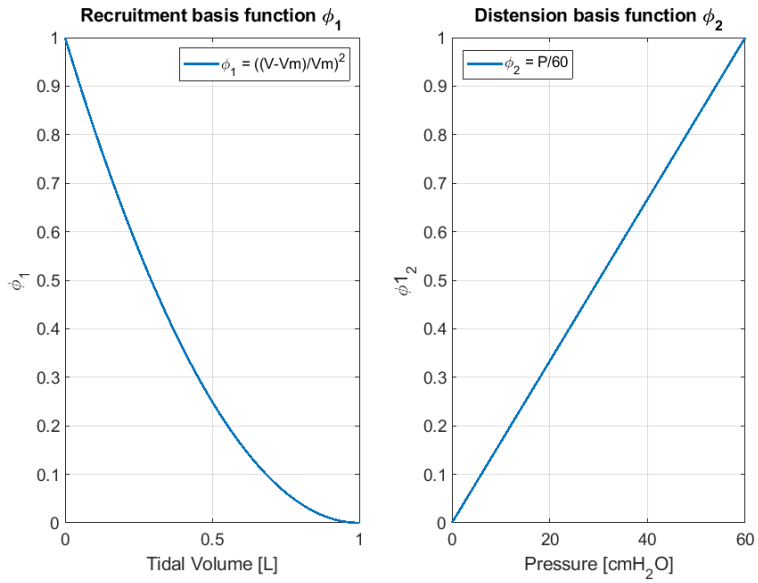

Figure 2.2: Recruitment and distension basis function shapes. (Both functions are dimensionless).

The recruitment basis function ϕ_1 captures the decreasing rate of recruitment alveoli based on positive volume delivered and is a piecewise function defined:

$$\phi_1 = \left(\frac{V - Vm}{Vm}\right)^2 \tag{2.4}$$

Where Vm is the upper limit of 1L in adults and ϕ_1 is set to 0 for $V > Vm$. The 1L limit should cover all adult tidal volume ranges as they are typically ventilated at 4-8ml/kg (Brower et al., 2000; Morton et al., 2019a). The distension basis function ϕ_2 captures lung distension at higher pressures, and is defined:

$$\phi_2 = \frac{P(t)}{60} \tag{2.5}$$

Using the basis function Eq 2.4 and Eq 2.5 into the single compartment model Eq 2.3, yields:

$$P_{aw} = E_1\phi_1 V + E_2\phi_2 V + RQ + PEEP \tag{2.6}$$

2.4 Time-varying Elastance Model

Many clinically applicable respiratory models assume patients are sedated and so their breathing is passive and fully controlled by the ventilator (Bates, 2009; Chiew et al., 2011). Therefore, during lower levels of sedation, patients may additionally show breathing effort, also known as spontaneous breathing (SB) effort, on top of the supported breathing by MV. Spontaneous breathing effort is the natural breathing performed by the patient and thus applies a negative pressure to the positive pressure provided by the ventilator. These spontaneous breathing efforts adds significant variability in respiratory mechanics. Therefore, additional methods are required to estimate patient effort to enable accurate identification of patient lung mechanics (Chiew et al., 2015a; Redmond et al., 2019). Figure 2.3 shows the negative pressure being added during a breath.

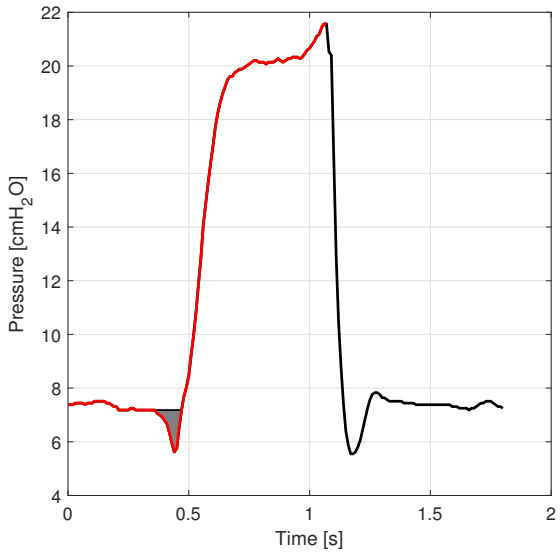

Figure 2.3: Pressure waveform of spontaneous breathing patient due to low sedation. Inspiration is shown in red, expiration in black and the pressure drop caused by SB is shaded.

Chiew et al. (2015a) proposed time-varying elastance model to utilise dynamic lung elastance to account for patient effort and identify patient-specific elastance (Chiew et al., 2015a). This model is derived from single compartment model (Eq 2.3) and is clinically applicable. This model lumps underlying lung mechanics as a single dynamic

lung elastance (E_{drs}). The E_{drs} represents the sum of elastic properties of alveoli (E_{rs}), patient-specific static chest wall elastance (E_{chest}) and elastance generated by patient effort (E_{demand}) and defined:

$$E_{drs} = E_{rs} + E_{chest} + E_{demand} \tag{2.7}$$

Replace E_rs from Eq 2.3 with E_{drs} from Eq 2.7 to account for patient effort:

$$P_{aw}(t) = R_{rs} \times Q(t) + E_{drs}(t) \times V(t) + PEEP \tag{2.8}$$

The $E_{drs}(t)$ is time dependent variable and thus cannot be used to compare across breaths and patients.

2.5 Model-based Ventilation in NICU

NICU ventilation strategies typically utilises lower PEEP settings but remain similar PIP. The respiratory rate is significantly different as adults receive 20 breaths/min but infants receive 60 breaths/min or higher. Infants are ventilated at low tidal volume settings 4-8ml/kg but due to their extremely small weight, the tidal volume delivered is small (Clark et al., 2000; Brown and DiBlasi, 2011; Sweet et al., 2010). For this reason, endo-tracheal tube (ETT) must be considered when modelling for neonates as the the small diameters of NICU ETT can significantly increase resistance to flow compared to adults (Kim et al., 2019a).

Jarreau et al. (1999) describes the pressure loss across the ETT. They used an empirical approach, where the pressure drop (ΔP_{ETT}) across the ETT is modelled (Jarreau et al., 1999):

$$\Delta P_{ETT} = L(0.0203D^{-4.25}Q^{1.5} + 0.319D^{-4}Q \tag{2.9}$$

Where L is the length of the ETT tube in cm, D is the diameter in mm, and Q is the flow rate in mL/s. Eq 2.9 assumes laminar flow. Turbulence occurs if the Reynolds number is above the critical value. In this case, the flow is always laminar for small ETT diameters (under 3.5 mm) (Jarreau et al., 1999), as turbulent,flow requires flow rates greater than 250 ml/s for an ETT diameter of 3.5 mm and typical NICU tidal volumes ranges are 5–20 mL (Sweet et al., 2010).

Thus, accounting for the pressure loss across the ETT, ΔP_{ETT} is added to the single compartment model from Eq 2.3 is:

$$P_{aw} = E_{rs}V + R_{rs}Q + PEEP + \Delta P_{ETT} \tag{2.10}$$

The basis function described in section 2.3 is used for adult MV data. This model can be adjusted to apply in the NICU cohort. For NICU infants, the basis functions are defined over a tidal volume range of 0-14 ml and pressure ranges 0-60 cmH_2O, which covers all likely NICU MV ranges. The 14 ml limit converts the typical adult volumes to the NICU size (Morton et al., 2019b). The pressure loss across ETT also needs to be considered for eq 2.6. Thus, yielding:

$$P_{aw} = E_1\phi_1 V + E_2\phi_2 V + RQ + PEEP + \Delta P_{ETT} \tag{2.11}$$

Neonates are ventilated at constant low PEEP (< 6 cmH_2O). Morton et al. (2019b) showed distension elastance is most significant, and most commonly identified, at higher PEEP levels. Therefore, it can be assumed infants would have minimal or no distension (E_2 =0). The ΔP_{ETT} measures the pressure drop across ETT and thus absorbs resistive term from original single compartment model eq 2.2, yielding:

$$P_{aw} = E_1\phi_1 V + PEEP + \Delta P_{ETT} \tag{2.12}$$

Time-varying elastance or dynamic lung elastance (E_{drs}) is an elastance term capturing patient inspiratory effort (Chiew et al., 2015a). The basis function in Eqs 2.4 and 2.5 capture all patient underlying tissue mechanics, but cannot capture patient effort. Edrs is derived from a time-varying elastance model used in adults (Chiew et al., 2015a), and is defined:

$$P_{aw} = E_{drs}(t) \times V(t) + E_1\phi_1 V(t) + PEEP + \Delta P_{ETT} \tag{2.13}$$

2.6 Summary

This chapter lists models used to identify patient-specific elastance throughout this thesis. The single compartment lung model is used to identify elastance (1/compliance) in sedated patients as MV fully controls patient breathing. The Basis function model is more complex model, that utilises basis functions, recruitment and distension function to identify both patient-specific elastance and lung distension in patients. The time-varying elastance model is a direct function of pressure, while implicitly dependent to time. The Edrs captures patient effort lumped with patient-specific lung condition.

CHAPTER 3

Clinical Data Cohorts

3.1 NICU CURE Kids Trial

The goal of the CURE Kids sponsored observational clinical trial was to retrospectively analyse neonatal lung mechanics. Clinical data from 10 invasively mechanically ventilated neonates were collected from Christchurch Women's Hospital Neonatal Intensive Care Unit (NICU). This trial was an observational trial, and thus no intervention was performed. Patients were treated using standard practice. Informed parental consent was obtained before data was collected. This study and the use of this de-identified data was approved by the New Zealand Northern B Health and Disability Ethics Committee (study ref:16/NTB/16). Ventilator pressure and flow profiles were collected for up to 24 hours under standard care conditions. Eligibility criteria included:

1. Expectation MV would continue for 24 hours
2. Clinical equipoise
3. General clinically assessed patient medical stability.

MV modes and settings were clinically determined as part of standard care. Patients received either conventional ventilation (CV) or high frequency oscillatory ventilation (HFOV) on a SLE5000 neonatal Ventilator (SLE, UK). Most patients received Patient Triggered Ventilation (PTV), although some were treated with more than one mode. Targeted Tidal Volume (TTV) is an "add on" specific to SLE, where pressure control is adapted breath-to-breath to improve attempts to meet tidal volume targets under pressure control.

None of the infants were sedated over the trial period, though some received morphine, which can have a sedative effect (Chase et al., 2004). In cases where an infant was re-intubated after weaning from MV, or the infant was later switched to another ventilation mode, a subsequent 24 hours of data recording was carried out with a second, further parental consent. Patient characteristics and relevant demographic data are shown in Table 3.1.

Ventilator data was recorded using MediCollector software (MediCollector, USA) on a laptop connected to Philips Healthcare MP70 bedside monitor (Philips Healthcare, NZ). The Philips bedside monitor was connected to the ventilator via a Vuelink M1032A respiratory module (Philips Healthcare, NZ). The equipment set-up is shown in Figure 3.1. Airway pressure (mbar) and flow (L/min) were recorded at a sampling rate of 125 Hz.The airway pressure and flow are converted into cmH_2O and mL/s in model fitting.

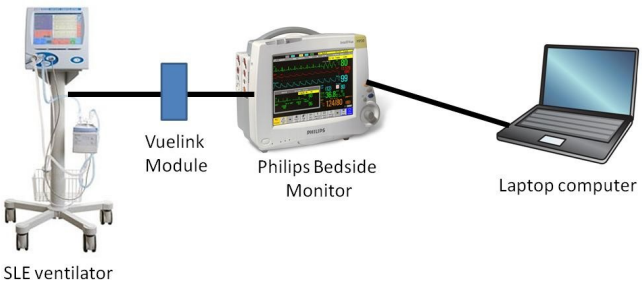

Figure 3.1: NICU clinical data recording set up and is a reproduction from Kim et al. (2019a).

Table 3.1: Clinical characteristics of recruited NICU patients

Patient	Ventilation Mode	Gender	Gestational Age at birth (weeks)	Post-natal age (days)	Weight(g)		Days of MV	Steroids			Surfactant therapy	Morphine		Clinical Notes
					Birth	Trial		Prenatal	Postnatal	During recording		Y/N	Dose [mcg/kg/h]	
1	HFOV	F	26.5	31	760	1120	22	Y	N	Y	N	Y	12	RDS, severe lung disease
2	HFOV	F	25	21	570		21	Y	Y	N	N	Y	?	Severe lung disease, previous sepsis/pneumonia
	CV - PTV + TTV			23		770	23			Y			PO	Severe RDS, CNS Sepsis, PPHN
	CV - PTV + TTV			32		890	27		N	N			PO/5**	
3	CV - SIMV + TTV	M	41.5	3	3400	3400	3	N	Y	?	N	Y	10	Severe Hypoxic Ischemic Encephalopathy, seizures
4	CV - PTV + TTV	F	37	2	2750	2750	2	N	N	-	N	Y	6	PPHN
5	HFOV	F	29.9	0	1580	1580	1	Y	N	-	Y	N	-	MCDA twin, Maternal Preeclampsia Toxaemia
	CV - PTV + TTV			2										
6	CV - PTV + TTV	M	27.4	2	1170	1170	1	Y*	N	-	N	Y	?	Oesophageal atresia, post op from surgery
7	CV - PTV + TTV	F	28.1	45	960	1990	5	Y	N	-	Y	Y	20	Abdominal surgery
8	CV - PTV + TTV	F	25.7	2	770	770	2	N	N	-	Y	N	-	RDS
9	CV - PTV + TTV	M	25.3	4	820	-	5	Y*	N	-	N	Y	?	RDS
10	CV - PTV + TTV	M	25.9	4	810	810	1	Y*	N	-	N	N	-	RDS

* Partial course only. ** oral changed to infusion at stated rate.

HFOV: High frequency oscillatory ventilation. CV: Conventional ventilation. PTV: patient triggered ventilation.

PSV: pressure support ventilation. TTV: Targeted tidal volume.

RDS: Respiratory Distress Syndrome. PPHN: Persistent pulmonary hypertension of the newborn.

CNS: central nervous system. MCDA twins: monochorionic diamniotic twin gestation.

NICU ETT diameter size are typically 3-5 mm. The diameter size of ETT is determined by patient weight as shown in Table 3.2. Clinically ETTs are shortened to an appropriate patient-specific length by 1-2 cm post-insertion, as clinically determined. The shortened length was unavailable for this study and thus, it was assumed that all ETTs are shortened by 2cm.

Table 3.2: Clinical guidelines for ETT selection

ETT diameter [mm]	Un-shortened ETT length [cm]	Indication for use
2.0	-	Cannot insert a 2.5 mm ETT
2.5	18	Weight $<$ 1.5 kg
3.0	19.5	Weight 1.5 - 2.5 kg
3.5	20	Weight 2.5 - 4.0 kg
4.0	-	Weight $>$ 4 kg

3.2 Pressure Support (PS) and Neurally Adjusted Ventilatory Assist (NAVA)

Spontaneously breathing (SB) patients undergo assisted spontaneous breathing (ASB) ventilation mode. ASB aims to assist weaning and is used until extubation as a step from fully controlled ventilation. Weaning is a critical procedure as the patient transition to spontaneously breathing and the ventilator assists that translation. Spontaneous breathing with supported MV breaths have been reported to have positive impact. SB patients have increased pulmonary gas exchange, systemic blood flow, and oxygen supply to the tissue (Burchardi, 2004; Putensen et al., 2005; Spahija et al., 2010; Brander and Slutsky, 2006; Freebairn and Hickling, 2005; MacIntyre, 1986). ASB mode is synchronised with patient breathing patterns and supports the breath. The amount of assist is ideally based on the patient's demand or triggers, and aims to reduce the overall work of breathing, thus supporting patient effort but not fully controlling it (Spahija et al., 2010; Tejeda et al., 1997).

Pressure support (PS) ventilation is a very common ASB ventilation mode. PS detects the pneumatic signal generated by the initial patient breathing effort, as measured in the ventilatory circuit with either pressure or flow. In particular, drop in pressure in the circuit at the commencement of a patient breath triggers the ventilator to provide sufficient added pressure, flow and PEEP to reduce the work of breathing and assist patient breathing. These parameters and settings are determined clinically (Spahija et al., 2010).

Neurally adjusted ventilatory assist (NAVA) is another, emerging assisted ventilation mode. NAVA utilises a directly measured Electrical activity of the diaphragm (Eadi) signal to determine patient demand. This measurement is made by a sensor on the endotracheal tube (ETT). The magnitude of this signal driving the breath determines the level of breath support it provides in the specific breath (Laghi, 2008; Sinderby et al., 2007, 2015).

Piquilloud et al. (2011) conducted a study comparing PS ventilation with the NAVA ventilation mode. They acquired data from 22 invasively mechanically ventilated patients from University Hospital of Geneva (Switzerland) and Cliniques Universitaires St-Luc (Brussels, Belgium). The study protocol involved a 20 minute continuous recording of patients airway pressure, Eadi and flow profile. Data are first measured in PS mode with clinically set parameters. PS was then switched to NAVA mode with the same parameters were measured for 20 minutes (Piquilloud et al., 2011). Patients were ventilated using a Servo-I ventilator (Maquet, Solna, Sweden) and data was sampled at 100 Hz using Servo-tracker V4.0 (Maquet, Solna, Sweden). Patient demographics and ventilator settings is seen in Table 3.3.

Table 3.3: Patient demographics and ventilator settings for PS and NAVA from Piquilloud et al. (2011)

Patients		
Age (years)	66 ± 12	
P/F ratio	194.8 ± 58.1 mmHg	
Ventilator Settings	**PS**	**NAVA**
FiO2	0.43 ± 0.17	0.43 ± 0.17
PEEP	7 ± 2	7 ± 2
Inspiratory Trigger	Flow Trigger: 1.2 l/min (20/22 Patients) Pressure Trigger: -4 and -5 cmH_2O (2/22 patients)	0.5 μV
Expiratory Trigger Sensitivity (ETS)	25-30%	-
PS Level	13 ± 3 cmH_2O	-
Pressurisation Slope	100-150 ms	-
NAVA Gain Level	-	2.2 ± 1.8 $cmH_2O/\mu V$

3.3 Summary

This chapter outlines the clinical cohorts and data collected. These cohorts and data are used throughout this thesis to examine models, methods, and lung mechanics in critically ill. The NICU cohort is especially unique as no similar data set currently exists for this cohort. The PS/NAVA adult cohort offers a unique opportunity to investigate the dynamics and characteristics of patient-specific breathing effort.

CHAPTER 4

Quantifying Patient effort in an Adult Cohort

4.1 Introduction

The estimation of patient-specific respiratory mechanics during mechanical ventilation (MV) can potentially help personalize and optimize therapy (Sundaresan et al., 2011; Amato et al., 2015; Major et al., 2018). In particular, the ability to estimate and monitor patient-specific respiratory mechanics enhances the understanding of patient-specific condition and leads to individualised care (Chiew et al., 2015a; Sundaresan et al., 2011). There are several methods to estimate the respiratory mechanics of a fully sedated MV patient, as the ventilator has full control of the patient's work of breathing (Sundaresan et al., 2011; Bates, 2009).

Compared to fully sedated patients, the respiratory mechanics of spontaneously breathing (SB) or patients whose work of breathing is only partially assisted by MV are much

more difficult to estimate. This difficulty is due to un-modelled and variable patient effort introduced into the system, obscuring the patient-specific response to the ventilator (Brochard et al., 2012). Model-based approaches for treating SB patients is not common because SB severely affects estimation of respiratory mechanics, which is also seen during asynchrony in MV patients (Major et al., 2016a; Damanhuri et al., 2016; Kannangara et al., 2016a; Chiew et al., 2018). However, as studies (Grinnan and Truwit, 2005; Chiew et al., 2015a) increasingly found partial ventilation or SB ventilation modes may be beneficial for patient recovery, there is a need for model-based approach for estimating patient-specific respiratory mechanics during SB.

Respiratory system mechanics can be modelled in different ways, ranging from simple models to complex multi-compartment models (Möller et al., 2011; Bates, 2009; Ben-Tal, 2006). Complex models can provide a more physiological representation of lung behaviour, but can be difficult to identify in the clinical environment without additional invasive measurements (Schranz et al., 2012a; Docherty et al., 2011). Therefore, the application of complex models are limited in the clinical environment (Chase et al., 2018; Morton et al., 2019a). Conversely, simpler models are easier to implement, but lack the ability to accurately represent all observed dynamics and physiology. Hence, models used in clinical settings should be a balance between both aspects.

This study utilises the time varying elastance model described in Chapter 2 (Eq (2.8)). This model can capture respiratory mechanics in SB patients. The time-varying trajectory of Edrs changes during a breath as a direct function of pressure and, implicitly, time, and has a negative component where measured airway pressure is decreasing, yet air is still flowing into the lungs due to un-modelled patient effort opening lung volume (Redmond et al., 2019). The dynamics of this time-varying model allows the capture of respiratory mechanics for both spontaneous breathing and sedated, fully controlled breathing to be captured (Chiew et al., 2015a,c).

In this study, the ability of the time-varying elastance model to capture SB respiratory mechanics is further investigated. Specifically, this study focuses on the negative elastance component of the model in SB patients and whether it can be used as a metric of patient effort. Two methods of quantifying negative elastance are presented to quantify negative elastance. Both methods utilise the time-varying elastance model as a basis. The ability to quantify negative elastance, and thus the patient input effort, as separate from the ventilator supported work of breathing, can lead to better understanding of patient breathing effort and lung condition, and thus be used to enhance MV therapy.

4.2 Methods

The Time-varying elastance model described in Chapter 2 section 2.4, Eq (4.1) is used to compare patient effort with Eadi. This equation is repeated in this chapter for clarity and ease as Eq (4.1), where the model is defined:

$$P_{aw}(t) = R_{rs} \times Q(t) + Edrs(t) \times V(t) + PEEP \tag{4.1}$$

Figure 4.2, repeated for clarity, from Figure 2.3 Chapter 2, shows during spontaneous breathing effort, patients apply negative pressure to the positive pressure provided. During this period, the $Edrs(t)$ would be negative, as shown by Chiew et al. (2015a). It is important to note, there is no physical 'negative elastance'. The negative elastance value in the identified model means there is a positive inspired volume response to an applied negative pressure created by the un-modelled patient effort opening the diaphragm to expand the lung, and thus creating the airflow. It is modelled and identified here as a negative elastance capturing patient effort.

Patient data is separated into individual inspiratory breaths and elastance is identified over inspiration. Inspiratory volume is calculated by integrating inspiratory flow with respect to time. The pressure (P), flow (Q), volume (V), and electrical activity of di-

aphragm ($Eadi$) (Piquilloud et al., 2011) signals are interpolated to 200 data points over this inspiratory data to allow direct comparison between breaths and patients.

$Edrs(t)$ is calculated from rearranging Eq (4.1), which yields:

$$Edrs(t) = \frac{P_{aw}(t) - RQ(t) - PEEP}{V(t)} \tag{4.2}$$

Taking the integral of $Edrs(t)$ yields in area under the curve (AUC) of $Edrs$ and is normalised with inspiratory time (Δt_i), to allow breath-to-breath comparison:

$$AUCEdrs = \frac{\int Edrs(t)\, dt}{\Delta t_i} \tag{4.3}$$

The normalised $AUCEdrs$ from Eq 4.3 is similar to a two point static elastance and can be used to describe patient-specific disease state (Chiew et al., 2015a):

$$AUCEdrs = Average\ \ E_{rs} \tag{4.4}$$

In this study, two methods are used to estimate the negative elastance component of $Edrs$ and $AUCEdrs$. The Zero Crossing method and the Trapezoidal method.

4.2.1 Zero-Crossing Method

The zero-crossing method is a straight forward approach in quantifying the negative $Edrs$. Zero-crossing points for when $Edrs$ changes from positive to negative and flow is greater than 50 ml/s. At the start of inspiration, flow and volume are very small, thus, any decrease in P_{aw} below PEEP results in very large negative values of $Edrs$, but is likely due to small measurement and computational errors. Therefore, flow less than 50 ml/s is discarded.

Once the negative $Edrs$ is calculated, the AUC of negative $Edrs$ region is used to find

patient effort. As shown in Figure 4.1, the two vertical red lines represents point where flow is greater than 50 ml/s and the zero-crossing of the $Edrs$ and the respective pressure, flow, $Eadi$, and $Edrs$ shown. This region between zero crossing and flow greater than 50 ml/s can be considered where patient demand elastance is greater than the elastance from the chest wall and lung, and eliminates only a very few data points likely influenced by ventilator dynamics and not the patient.

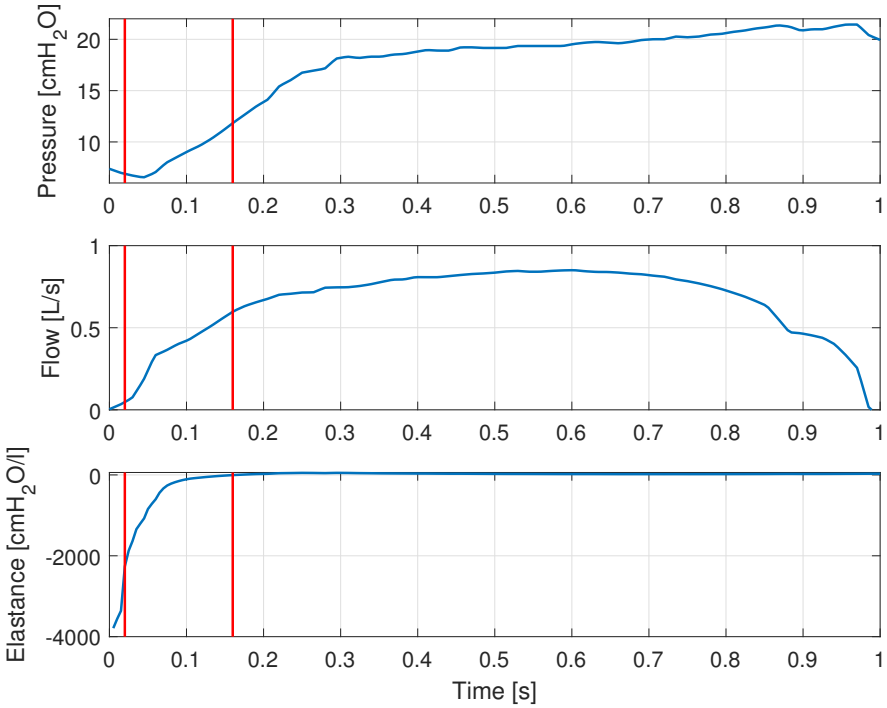

Figure 4.1: Inspiratory Pressure, Flow, $Eadi$, and $Edrs$ with respect to normalised time with zero-crossing method region

4.2.2 Trapezoidal Method

The small drop in pressure before recovering due to patient effort is seen in Figure 4.2, which is a repeat of Figure 2.3. This drop is clearly visible as the blue line is measured inspiratory pressure, the black line is expiratory pressure and the area shaded in grey shows potential patient effort as this region results in negative elastance using the model defined. This is used to quantify the AUC of the shaded region in Figure 2.3. The elastance value is identified from the time-varying elastance model of Eq (4.2). This method

utilises AUC of pressure, volume and flow, rather than the $AUCEdrs$ is calculated from it.

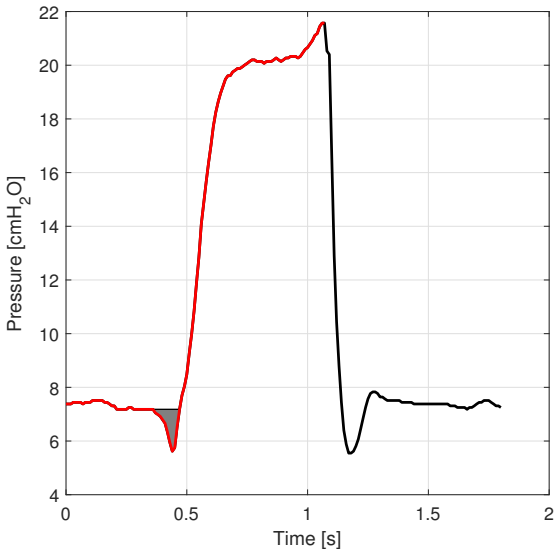

Figure 4.2: Repeat of Figure 2.3, Pressure waveform with small drop caused by patient's spontaneous breathing effort (shaded). Red is inspiration and black is expiration.

Integrating each of the components of the single compartment model yields the following equation:

$$\int P_{aw}(t)\,dt = E_{rs}\int V(t)\,dt + R_{rs}\int Q(t)\,dt + PEEP\int dt \tag{4.5}$$

From Eq (4.5), the normalised $AUCEdrs$ can be substituted for E_{rs} to yield:

$$\int P_{aw}(t)\,dt = AUCEdrs\int V(t)\,dt + R_{rs}\int Q(t)\,dt + PEEP\int dt \tag{4.6}$$

From this model, the area where pressure drops in Figure 4.2, and is then restored to starting PEEP is defined:

$$Area_{negative\ pressure} = \int_0^N P_{aw}\,dt \quad WhereEdrs \leq 0 \tag{4.7}$$

Thus:

$$Area_{negative\ pressure} = AUCE_{neg} \times Area_{volume} + R \times Area_{flow} \tag{4.8}$$

Rearranging Eq (4.8) results in:

$$E_{negative} = \frac{Area_{negative\,pressure} - R \times Area_{flow}}{Area_{volume}} \tag{4.9}$$

Thus, negative elastance contribution is proportional to patient effort and can be defined:

$$AUCE_{negative} \approx \lim_{Edrs<0} \frac{\int P_{aw}(t)\,dt - R\int Q(t)\,dt - PEEP\int dt}{\int V(t)\,dt} \tag{4.10}$$

4.2.3 Clinical Patient Data

The PS and NAVA patient cohort detailed in Chapter 3 Section 3.2 is used in this study. 22 invasively mechanically ventilated patients were recorded using PS and NAVA ventilation modes. Patients were recorded initially with PS mode for 20 minutes and subsequently switched to NAVA mode for another 20 minutes. Patients had their electrical activity of diaphragm measured during the data recording (Piquilloud et al., 2011). This chapter only utilises NAVA patient data.

4.2.4 Analysis of Negative Elastance Metric

$AUCEdrs$ values calculated using both methods are compared. Negative $AUCEdrs$ values are normalised by the median values and the absolute values are recorded. The Bland-Altman plot is used to check for bias between these two methods (Altman and Bland, 1983). The two methods are compared with the measured peak $EAdi$ signal using Pearson's correlation coefficient to compare to a physiological measure of diaphragm muscle activation. Eadi is thus taken as a measure of patient inspiratory effort, where peak Eadi and AUC Eadi are effectively the same (Moorhead et al., 2013). Note, because EAdi can vary between patients due to sensor placement and other factors, comparing between patients is not possible.

The coefficient of variation (CV) for each $AUCEdrs$ estimation method is also calculated.

The CV values will allow better understanding of variability of the negative elastance component analysed. Comparing the two variability metrics will show how much variations could exist in negative elastance results.

4.2.5 Positive Elastance

The zero-crossing method and trapezoidal methods are metric to quantify patient effort which, occurs at the start of inspiration while SB is present. The positive patient elastance is calculated by taking AUC of $Edrs$ from the positive portion of $Edrs$ trajectory. This positive trajectory of $Edrs$ is the passive lung dynamics as ventilator takes over patient breathing and thus, positive $AUCEdrs$ is a measurement of patient-specific lung elastance in response to MV.

4.3 Results

Table 4.1 summaries results for both methods, includes negative and positive AUCEdrs using two methods and normalised AUCEdrs. This table also includes the CV of negative AUCEdrs values. The median [Interquartile Range (IQR)] of zero-crossing point across all patient is 32.5 [26-39] and median [IQR] of flow $>$ 50 ml/s was 5 [4 - 9]. The normalised negative AUCEdrs values of -3.29 [-4.80 - -2.50] cmH_2Os/l for the zero-crossing method and –1.90 [-2.36 - -1.66] cmH_2Os/l for the trapezoidal method. The absolute valued CV of negative AUCEdrs across all patients is: 0.18 [0.15 - 0.26] cmH_2Os/l for the zero-crossing method and 0.15 [0.13 - 0.23] cmH_2Os/l for the trapezoidal method.

Figure 4.3 shows scatter plots of positive AUCEdrs normalised values using both methods for Patients BRU2, BRU10 and GE07. The minimum correlation coefficient value over all patients is R = 0.84, median is R = 0.98, and maximum correlation coefficient is R = 0.99. These results show the two methods can capture positive elastance correctly and similarly. Therefore, they both should be able to quantify the negative elastance

Table 4.1: Summary of zero-crossing method and trapezoidal method (25^{th}, 50^{th}, 75^{th})

	Zero-Crossing method			Trapezoidal method		
	25^{th}	50^{th}	75^{th}	25^{th}	50^{th}	75^{th}
Negative AUCEdrs [cmH_2O/l]	-61.58	-48.09	-42.76	-133.99	-116.26	-94.33
Negative AUCEdrs normalised	-4.80	-3.29	-2.50	-2.36	-1.90	-1.66
Positive AUCEdrs [cmH_2O/l]	19.29	24.21	27.46	21.09	26.84	31.17
Costive AUCEdrs normalised	0.11	0.14	0.17	0.12	0.16	0.19
CV of Negative AUCEdrs	0.15	0.18	0.26	0.13	0.15	0.23

component.

Figure 4.4 shows the Bland-Altman plot for individualised patients who have no bias between the two methods, a small bias, and a clear bias. Most patients have the AUCEdrs calculated using two methods lie within 95% confidence interval, the example of can be seen in Figure 4.4, for Patients BRU10, BRU6, BRU11, and BRU12. Some of the patients, such as Patients GE08 and BRU14 shows a clear bias as either the difference would increase or decrease as mean increases as the value increases.

Figures 4.5 and 4.6 shows scatter plots of Eadi signal and negative AUCEdrs calculated using the two methods. The median [IQR] of R values calculated across patients are -0.01 [-0.27 - -0.14] for zero-crossing method and -0.04 [-0.29 - 0.07] for trapezoidal method. It is clear, the correlations are not strong, but the plots are patient-specific.

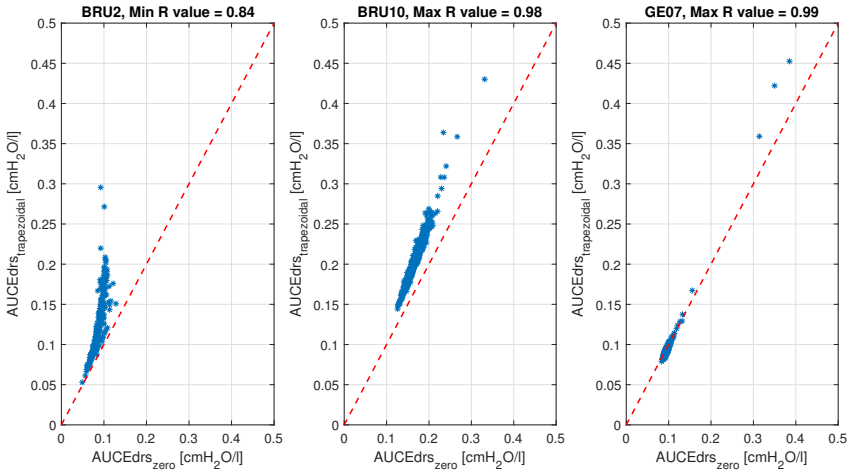

Figure 4.3: Comparison of positive AUCEdrs values from each method. left). Shows lowest correlation coefficient, Middle). Shows median correlation, and right). shows highest correlation.

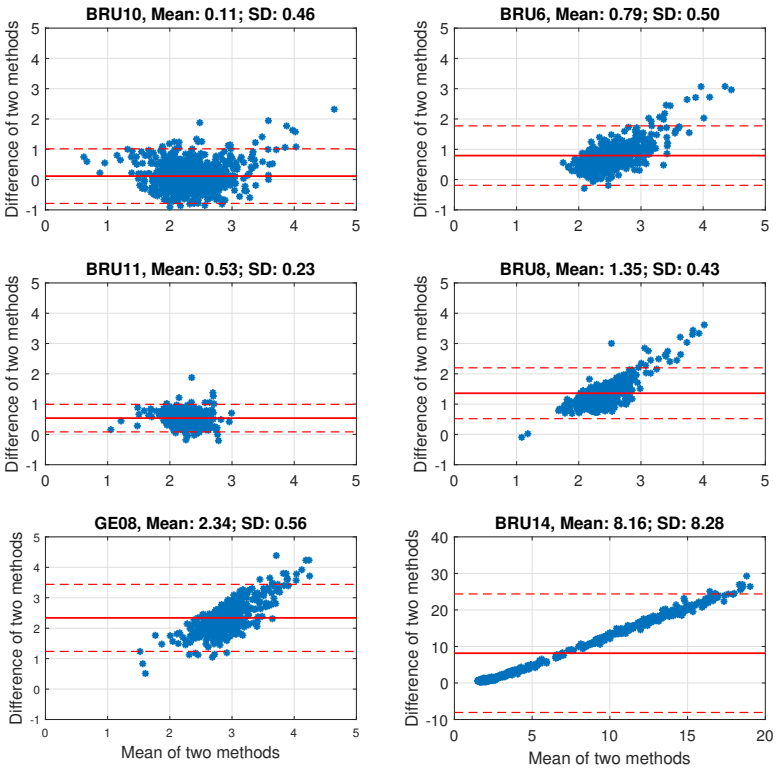

Figure 4.4: Bland-Altman plot of negative AUCEdrs using zero-crossing and trapezoidal method for cases where no bias exists to where clear bias exists (Altman and Bland, 1983).

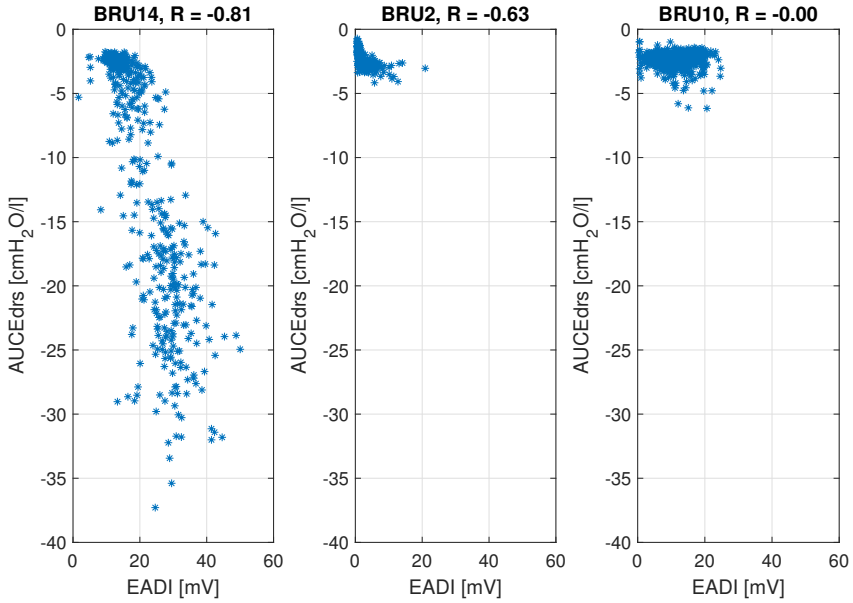

Figure 4.5: Samples of peak Eadi signal vs Negative AUCEdrs using zero-crossing method with different Pearson's correlation. Left). High Middle). Medium, Right). Low.

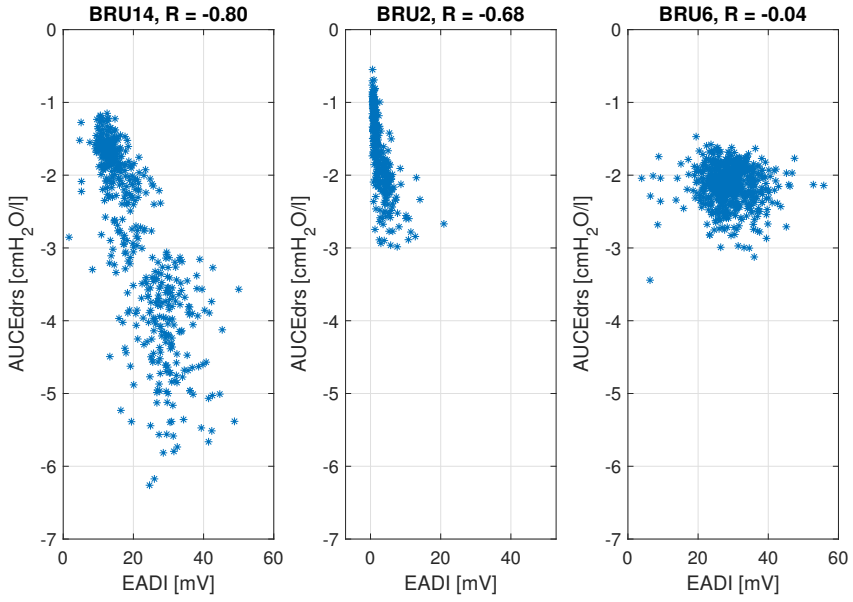

Figure 4.6: Samples of peak Eadi signal vs Negative AUCEdrs using trapezoidal method with different Pearson's correlation. Left). High Middle). Medium, Right). Low.

4.4 Discussion

The estimated normalised negative AUCEdrs values for the trapezoidal method is lower than zero-crossing method (42.26%). As shown in Table 4.1, the median of median AUCEdrs value and IQR of median is shown to be lower. Similar behaviour was also found in positive AUCEdrs where the AUCEdrs of the trapezoidal method have higher value.

The median [IQR] of zero-crossing index for all patients is: 32.5 [26-39] or 16.25% [13-19.5%] of the data. This result shows that the first 16.25% of inspiratory data represents negative elastance contributions primarily and 83.75% of the data makes up for positive AUCEdrs. This result holds considering the primary driver of overall observed behaviour.

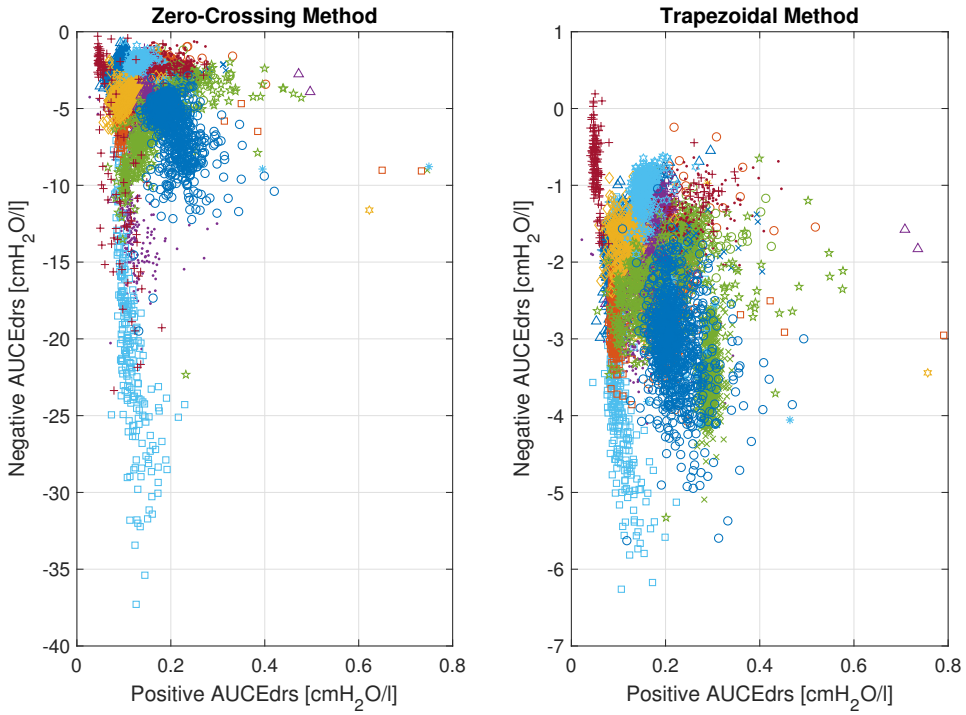

Figure 4.7: Scatter plot of Negative AUCEdrs with corresponding positive AUCEdrs for all patients. Left). Zero-crossing method, Right). Trapezoidal method.

Negative elastance values are compared with positive value to see if there are any relationship between the two. From Figure 4.7, it is clear that the negative AUCEdrs does not correlate with positive AUCEdrs as the median IQR of R = 0.18 [-0.43 - 0.40] for the

zero-crossing method and R = 0.19 [-0.16 - 0.29] for the trapezoidal method. This result is somewhat expected where negative AUCEdrs is a metric and a measurement of patient-specific SB effort, whereas positive AUCEdrs is a measure of patients-specific lung condition in response to MV. The amount of patient effort has little influence on the lung condition, but is more a function of patient's sedation state and how they respond to MV treatment.

Flow less than 50ml/s is not removed for the trapezoidal method because the initial assumption was that the small drop in pressure is the negative elastance component. The drop in pressure is very small and thus removing small amount of data at the start of already small section of the breath would result in removing large portion of negative elastance.

The $Eadi$ is unreliable due to the fact, the placement of these sensors vary from patient-to-patient as it would be placed on general approximate location and that it is also signal processed voltage measurement. Therefore can lead to amplifying even noise signal.

$Eadi$ is an electrical input to a biochemical to physical response of the muscle. This response is at least a second order system (coupled 1^{st} order equation), which implies a phase shift of 180° and thus a measurable time lag as the outcome muscle motion leading to breathing will be the convolution solution of this second order (or more) system in response to $Eadi$ input

Finally, every muscle may respond differently, for example due to level of sedation, to a given electrical $Eadi$ input. There is thus a sensitivity to this response that is patient specific and sedation specific (At minimum). Plus, humans are horribly variable!

All these factors reduce the viability of $Eadi$ as a metric correlating well to breathing

activity or action. We measure output action of breathing and $Eadi$ is the electrical input, they are not proportional or directly comparable for the reasons above, outside of very broad comparison

One of the main limitations of this study is that the only measurable metric available to validate the negative Edrs values is through using Eadi. Eadi is the electrical signal to trigger a diaphragm movement. However, as the Eadi signal is a processed signal, these data in some cases, may not be representative of the patient's actual demand (Piquilloud et al., 2011). Further variation in Eadi can arise due to exact sensor location and placement. Further, Eadi may also reflect a saturated signal, where any value over a level trigger activity. Thus, much of its value may not capture patient-specific demand. Hence, may not be a gold standard to assess patient-specific effort.

It is important to further verify the patient-specific demand elastance (negative Edrs) using other approaches, such as an oesophageal pressure measurement to investigate the pleural pressure changes in response to negative elastance, which would be a more true signal of patient-specific demand. Equally, since rising demand could indicate the potential to reduce support or wean the patient, an outcome assessment or successful reduction or weaning could better validate the clinical utility of these metrics.

4.5 Summary

Negative elastance is a conceptual component in time-varying elastance during MV breathing. It can be used to quantify patient's direct involvement/demand during breathing. However in this study, when attempting to quantify this it was shown to be clinically inapplicable as negative AUCEdrs captures more than only patient effort. Further research is needed to better validate any use of this metric against a true gold standard measure of patient effort to observe patient effort.

CHAPTER 5

Quantifying patient effort in an adult cohort using basis functions

5.1 Introduction

In Chapter 4, patient effort was quantified using two methods, the zero-crossing and trapezoidal methods. These methods were applied to a time-varying elastance model Chiew et al. (2015a) to capture spontaneous breathing effort (Kim et al., 2017), where a negative elastance in assumed to largely represent patient effort (Chiew et al., 2015a). However, results in Chapter 4 showed the use of Edrs did not align fully with electric activity of the diaphragm (Eadi) as it was not able to fully differentiate between patient-specific lung condition and patient effort. Chapter 4 concluded a different method would be needed.

Morton et al. (2019b) utilised basis function models to identify patient-specific alveoli recruitment and distension, as well as providing accurate prediction of lung mechanics after MV changes (Morton et al., 2018, 2019b,a). The basis functions use defined shapes to identify desired lung mechanics parameters over volume and pressure, enabling prediction. In particular, the alveolar recruitment basis function used in Morton et al. (2019b) identifies patient-specific alveoli recruitment in comparison to the single compartment model (Bates, 2009), which identifies lung elastance and can not differentiate heterogeneity of the lung or active patient effort (Bates, 2009).

More specifically, these models capture passive lung mechanics well in response to ventilator inputs. However, currently they cannot capture (un-modelled) patient-specific breathing effort, as seen in prior studies using these models to identify and manage asynchrony (Newberry et al., 2016; Kannangara et al., 2016a; Chiew et al., 2015b, 2018). Thus, there is a need to combine existing models with different approaches in order to assess both lung condition and patient breathing effort.

In this chapter, the recruitment basis function model of Morton et al. (2019b) is combined with time-varying elastance to separate lung condition and mechanics from spontaneous breathing effort. This approach is applied to data from patients under neurally adjusted ventilatory assist (NAVA) ventilation, as described in Chapter 3 (Piquilloud et al., 2011; Moorhead et al., 2013; Chiew et al., 2013). The aim is for the recruitment basis function model to capture lung mechanics, while the time-varying elastance model reflects the negative pressure dynamics of patient effort in addition to these mechanics (Chiew et al., 2015a; Morton et al., 2019b).

5.2 Methods

5.2.1 Patient Cohort and Acquisition

Mechanically ventilated data from 22 patients on NAVA as, described in Section 3.2, is analysed in this chapter. In this cohort, patients were initially ventilated using pressure support (PS) mode for 20 minutes and than switched to subsequent 20 minutes on NAVA. The electrical activity of diaphragm (Eadi), pressure, flow data were recorded (Piquilloud et al., 2011). Only the NAVA cohort is analysed in this analysis as NAVA mode adjusts input and thus resulting tidal volume in proportion to breathing effort (Morton et al., 2019b; Chiew et al., 2015a) whereas the pressure support mode delivers a set pressure in response to patient breath triggering. Hence, these patients and this mode provide data where tidal volume and effort are in proportion, which can be used to evaluate the resulting modelling approach to estimate patient-effort.

5.2.2 Model Fitting

A linear single compartment model described in Section 2.2 Eq (2.3) is modified for use with recruitment and distension basis functions in this analysis. The single compartment model is repeated here for clarity and reading ease, and is defined:

$$P_{aw} = E_{rs}V + R_{rs}Q + PEEP \tag{5.1}$$

Where, P_{aw} is the airway pressure, E_{rs} is the elastance of the lung, V is the volume, R_{rs} is the airway resistance, Q is the flow, and $PEEP$ is the pressure offset.

The single compartment model from Eq (5.1) is modified using basis functions described in Section 2.3 to identify alveoli recruitment and distension basis functions (Morton et al., 2019b). The shape of these basis functions is also repeated from Figure 2.2 as Figure 5.1 for ease. The recruitment basis functions is repeated from Chapter 2, Eq (2.4)

in this chapter as:

$$\phi_1 = \left(\frac{V - Vm}{Vm}\right)^2 \tag{5.2}$$

Where Vm is the upper limit of 1L in adults and ϕ_1 is set to 0 for $V > Vm$. The 1L limit should cover all adult tidal volume ranges, as they are typically ventilated at 4-8ml/kg (Brower et al., 2000; Morton et al., 2019b). And the distension basis function is repeated from Chapter 2, Eq (2.5) as:

$$\phi_2 = \frac{P(t)}{60} \tag{5.3}$$

The two basis functions are added to single compartment model, repeated from Eq (2.6):

$$P_{aw} = E_1\phi_1 V + E_2\phi_2 V + RQ + PEEP \tag{5.4}$$

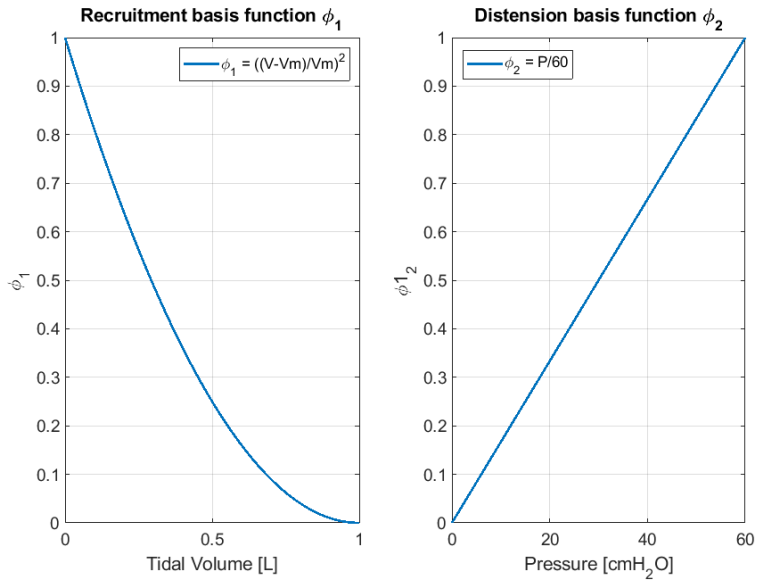

Figure 5.1: Recruitment and distension basis function shapes. (Both functions are dimensionless) repeated from Chapter 2 Figure 2.2.

The NAVA patient cohort were on a partial ventilation mode where the ventilator supports patient breathing based on their Eadi. Therefore, it is assumed, there was no distension, and the distension basis function is ignored in this analysis to improve identi-

fiability. This assumption leaves:

$$P_{aw} = E_1\phi_1 V + RQ + PEEP \tag{5.5}$$

Figure 5.2 shows an example of inspiration of pressure, flow and Eadi. In this figure, the pressure drop caused by spontaneous breathing effort is clearly visible at the beginning of the supported breath. The model identified in Eq (5.5) is defined to capture only passive breathing mechanics, and does not account for spontaneous breathing effort. This means the early spontaneous breathing efforts would hinder model fitting, as no specific ”shape” in pressure for spontaneous breathing effort. As a result, the 30% to 70% range of inspiration data (shown in red dashes) is used to identify patient-specific elastance, E_1 from Eq (5.5), as this range is expected to better reflect the pressure-volume lung recruitment dynamics, without the significant non-linear inspiratory drive seen at the start of the breath.

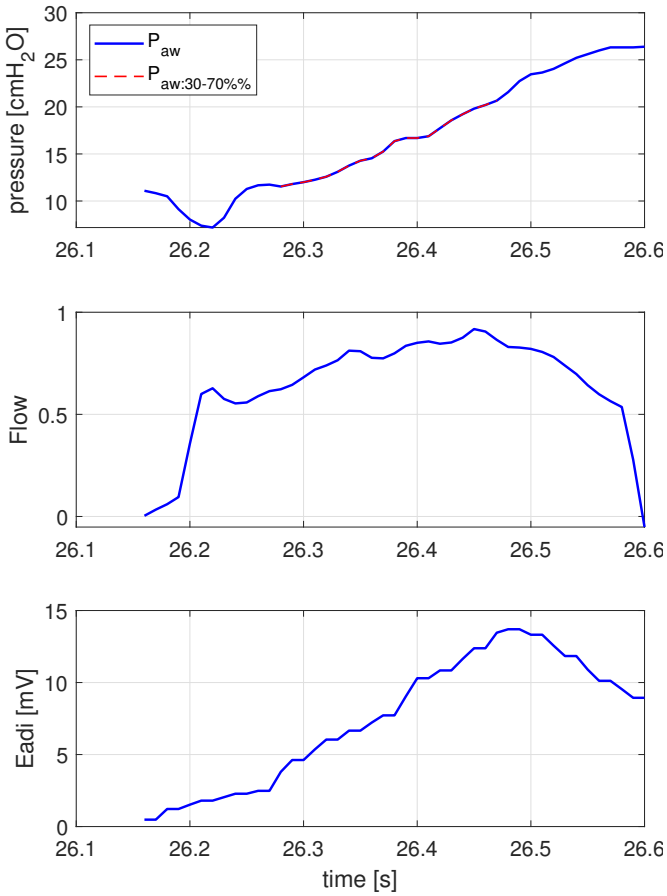

Figure 5.2: Example of pressure and flow with basis function model fit region (Patient 22)

Spontaneous breathing effort is quantified using the time-varying elastance model defined in Chapter 2. The time-varying elastance model utilises dynamic lung elastance, $Edrs$, which, is a sum of lung elastance and patient demand elastance. For this reason, $Edrs$ is identified from the error after the initial model fit from Eq (5.5). This two-step approach results in final equation defined:

$$P_{aw} = E_1\phi_1 V + RQ + PEEP + Edrs(t) \times V \tag{5.6}$$

where $Edrs(t)$ is defined:

$$Edrs(t) = \frac{P_{aw}(t) - P_{Modelfit}(t)}{V(t)} \tag{5.7}$$

This $Edrs$ term essentially absorbs all model-fit error of the 'expected' passive breathing

dynamics defined by the recruitment basis function. Thus, the $Edrs$ component is able to capture patient effort where it is defined as ($Edrs(t) < 0$), after identifying the underlying 'passive' lung mechanics. Edrs is expected to approach 0 as inspiration comes to an end, where E_1 becomes the dominant factor in determining airway pressure. Taking the area under the curve (AUC) of $Edrs$ is denoted $AUCEdrs$, which quantifies this time-dependent term and allows direct comparison between breaths and patients. Since patient effort is defined as negative $Edrs$ ($Edrs < 0$), taking the $AUCEdrs$ of negative component is assumed to capture patient effort.

5.2.3 *Edrs* Analysis

Preliminary analysis and data plotting showed many breaths start with fluctuations in pressure before the NAVA modes support becomes dominant where spontaneous breathing effort may also vary. Figure 5.3 shows small fluctuations in pressure at the start with low flow, which mathematically, causes $Edrs$ to be positive in a very short portion ($\leq$ 0.05 secs) during very early portion of inspiration. In Figure 5.3, the blue $Edrs$ curve is the original $Edrs$ curve calculated through fitting from Eq (5.7). However, due to these fluctuations, which may be caused by sensor sensitivity or other factors because the lung does not respond that quickly, $Edrs$ is positive. Thus, there is reason to believe these $Edrs$ values should be zero or negative and is only positive due to quantised data points, where physiologically, the patient is trying to breath in. Thus, the early section of $Edrs$ is adjusted using all subsequent points within first 10% of inspiration data is interpolated. This approximation allows estimation of a model-based 'true' patient demand.

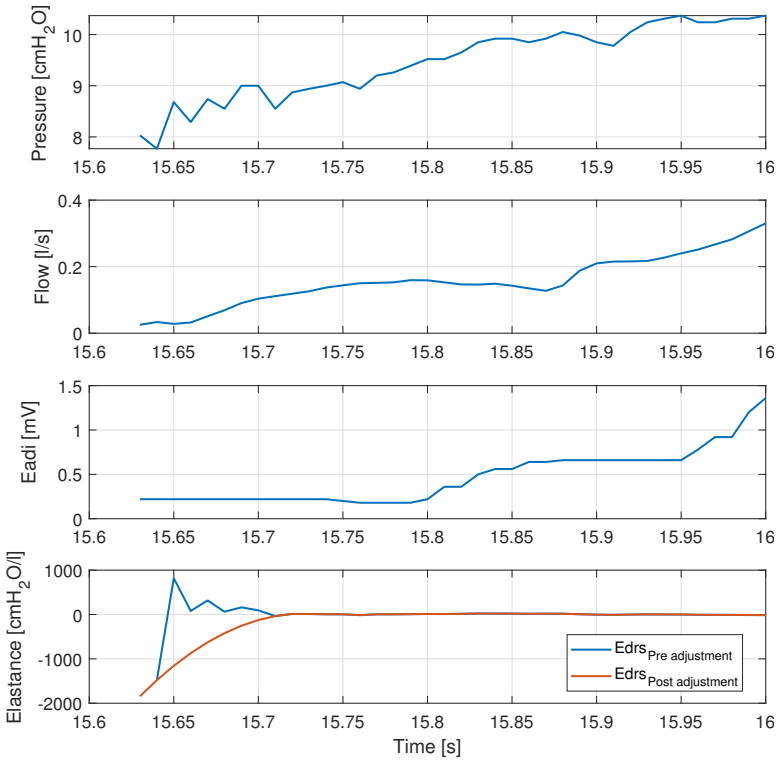

Figure 5.3: Example of Edrs adjusted

5.2.4 Analyses

Model fit and patient effort are presented and analysed as median and interquartile range (IQR). Scatter plots comparing $AUCEdrs$ with resulting tidal volume is used to compare the relationship between tidal volume and patient effort. Prior work by Moorhead et al. (2013) showed good correlation between $Eadi$ and tidal volume despite the muscle dynamics between $Eadi$ input and tidal volume response (Moorhead et al., 2013). Thus, comparing tidal volume and $AUCEdrs < 0$ compares these input to the clinically relevant output. Tidal volume and patient demand for oxygen should be correlated as the higher the patient demand, larger tidal volume is delivered to the patient by the ventilator.

5.2.5 Asynchrony

Preliminary results showed some patients exhibit asynchronous breaths. An example of one such breath is shown in Figure 5.4. The pressure waveform of these breaths

typically rises then falls as patient demand becomes greater than ventilator driven mechanic. In this figure, pressure rises but flow is low and Eadi is also very small, and thus indicates patient-ventilator asynchrony. In this chapter, asynchronous breaths are noted and will be presented as percentage of the total number of breaths per patient.

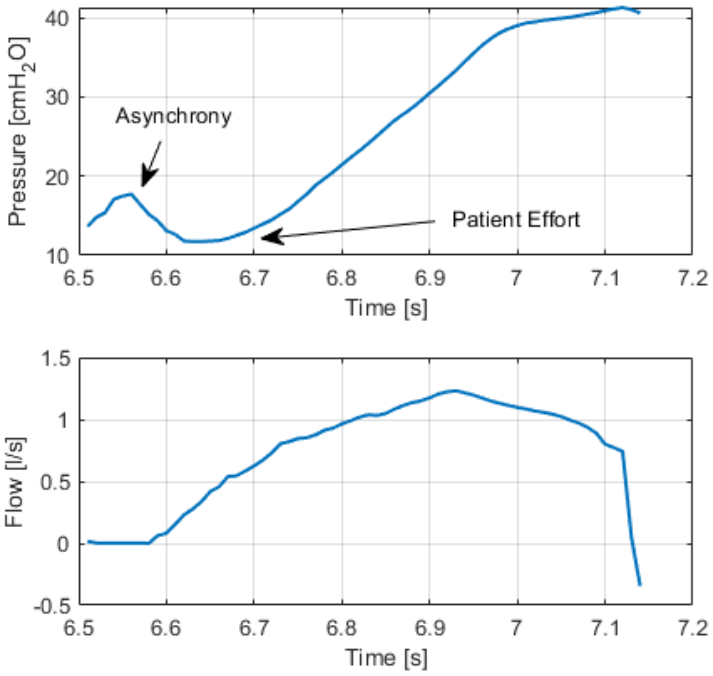

Figure 5.4: Example of Asynchronous breath from Patient 22

5.3 Results

5.3.1 Model Fit

Model fit using basis functions on NAVA data was good and the use of $Edrs$ captured expected spontaneous breathing effort. Figure 5.5 shows how the model with basis function and $Edrs$ is able to capture a typical example breath. In this figure, it is also clear, how the shape of the NAVA pressure waveform is close to being linear rather than a ramp or square waveforms generally seen in fully controlled ventilation modes (Bates, 2009; Chiew et al., 2011; Kim et al., 2019a; Chiew et al., 2015a). Figure 5.6 shows zoomed Edrs plot from Figure 5.5. This figure shows the negative $AUCEdrs$ range, shaded in

orange and positive $AUCEdrs$ region shaded in purple.

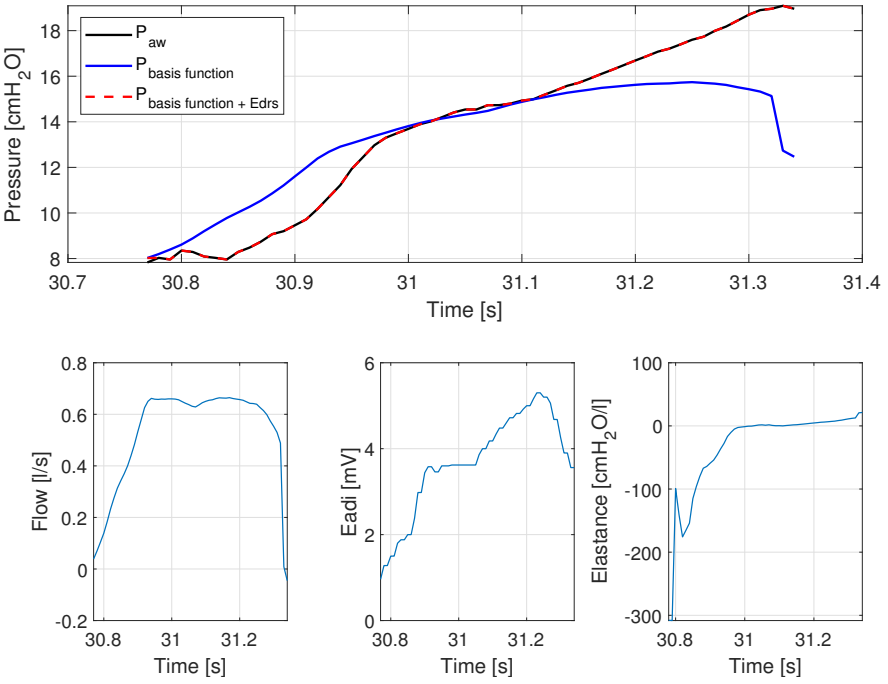

Figure 5.5: Example breath with model fit

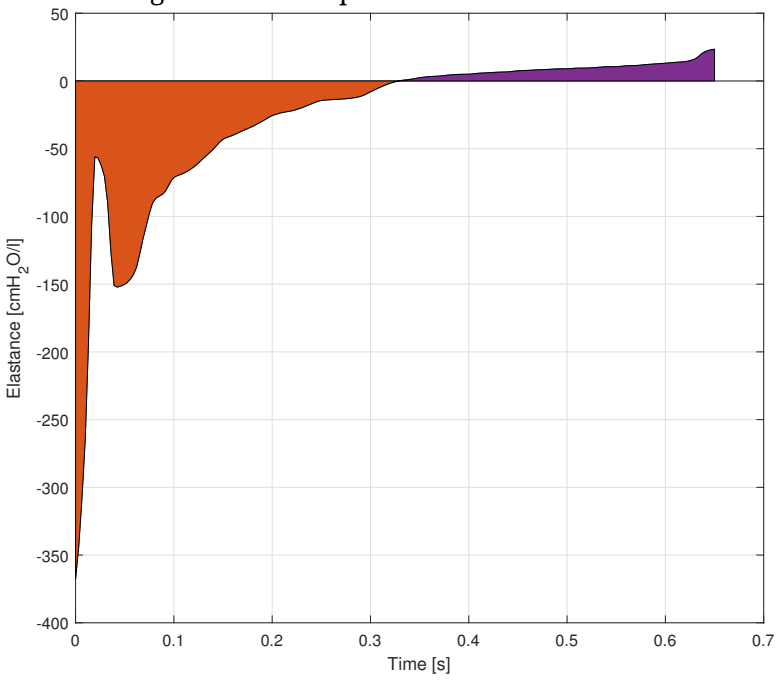

Figure 5.6: Zoomed $Edrs$ plot from Figure 5.5. Negative $Edrs$ is shaded in Orange and positive is shaded in purple.

5.3.2 Patient breathing Effort

Table 5.1 shows $E1$, negative $AUCEdrs$, Median AUCEdrs, and tidal volume. Overall, the median [IQR] of recruitment basis function fit, E_1, across this cohort was 46.14 [27.38 - 71.85] cmH_2O/l which is within typical ranges seen for MV patients (Morton et al., 2018, 2019b,a). The quantified negative AUCEdrs was -33.49 [-52.15 - -20.09] cmH_2O/l. The median [IQR] of settling positive $AUCEdrs$ is 14.78 [8.97 - 19.77] cmH_2O/l. The median IQR of tidal volume was 0.43 [0.35 - 0.5]l across this cohort.

Patient 16 had the lowest median [IQR] basis function model fit with 11.99 [7.38 - 18.25] cmH_2O/l, while Patient 19 was highest with 99.27 [87.69 - 109.5] cmH_2O/l. Patient 22 had the highest negative AUCEdrs value with -102.21 [-406.36 - -44.91] cmH_2O/l, whereas Patient 12 had lowest negative AUCEdrs with -10.00 [-31.36 - -3.95]cmH_2O/l.

Table 5.1: Model Fitting Results

Patient	E1 [cmH_2O/l]	Negative AUCEdrs [cmH_2O/l]	MedianAUCEdrs [cmH_2O/l]	Vt [l]
1	31.14 [25.61 - 36.29]	-48.88 [-58.29 - -41.67]	12.84 [11.20 - 15.00]	0.63 [0.59 - 0.67]
2	33.10 [25.79 - 40.41]	-52.38 [-59.96 - -45.11]	20.26 [17.37 - 23.32]	0.46 [0.43 - 0.50]
3	41.68 [34.06 - 50.98]	-34.52 [-45.29 - -28.85]	16.97 [14.14 - 20.11]	0.39 [0.36 - 0.43]
4	17.39 [10.86 - 28.12]	-32.17 [-55.70 - -21.58]	2.28 [0.90 - 4.67]	0.31 [0.29 - 0.34]
5	61.88 [42.77 - 75.33]	-59.63 [-68.28 - -52.06]	24.90 [20.60 - 29.61]	0.38 [0.35 - 0.41]
6	17.74 [10.02 - 28.21]	-14.28 [-22.40 - -10.97]	7.52 [6.15 - 9.39]	0.46 [0.42 - 0.49]
7	60.42 [47.51 - 75.81]	-21.29 [-36.78 - -10.07]	7.59 [0.89 - 20.22]	0.28 [0.18 - 0.48]
8	25.63 [8.58 - 56.79]	-88.28 [-130.54 - -61.25]	7.53 [2.39 - 11.80]	0.56 [0.37 - 0.94]
9	80.57 [66.89 - 97.55]	-43.64 [-50.07 - -35.44]	20.06 [13.39 - 25.26]	0.47 [0.34 - 0.52]
10	26.10 [16.18 - 36.22]	-30.18 [-38.55 - -24.68]	17.73 [15.40 - 20.26]	0.42 [0.39 - 0.44]
11	35.47 [29.09 - 42.63]	-27.64 [-33.01 - -24.03]	16.87 [14.51 - 19.46]	0.42 [0.38 - 0.48]
12	67.39 [58.23 - 79.43]	-10.00 [-31.36 - -3.95]	3.26 [-1.15 - 6.99]	0.29 [0.26 - 0.33]
13	12.67 [5.97 - 24.56]	-32.20 [-38.26 - -27.60]	15.77 [12.33 - 18.10]	0.50 [0.47 - 0.53]
14	43.02 [32.37 - 60.51]	-40.69 [-50.52 - -33.30]	16.66 [10.94 - 22.40]	0.43 [0.14 - 0.57]
15	90.37 [77.30 - 107.92]	-28.73 [-36.89 - -23.10]	17.09 [13.96 - 22.16]	0.54 [0.47 - 0.61]
16	11.99 [7.38 - 18.25]	-23.33 [-33.62 - -9.20]	14.66 [12.95 - 17.15]	0.62 [0.59 - 0.65]
17	28.04 [16.88 - 41.04]	-29.33 [-40.63 - -21.90]	12.98 [10.62 - 16.01]	0.48 [0.37 - 0.58]
18	71.00 [59.50 - 83.95]	-18.82 [-30.24 - -10.53]	9.84 [5.59 - 14.22]	0.44 [0.34 - 0.52]
19	99.27 [87.69 - 109.50]	-3.55 [-10.35 - -1.80]	2.84 [-1.97 - 8.54]	0.29 [0.24 - 0.34]
20	54.75 [48.62 - 60.66]	-14.84 [-25.37 - -10.49]	9.46 [6.61 - 11.94]	0.43 [0.38 - 0.49]
21	12.48 [3.54 - 55.49]	-43.05 [-54.17 - -31.99]	13.30 [9.91 - 17.30]	0.77 [0.66 - 0.87]
22	71.03 [54.81 - 86.99]	-102.21 [-406.36 - -44.91]	19.56 [15.11 - 24.07]	0.44 [0.40 - 0.48]
All	46.14 [27.38 - 71.85]	-33.49 [-52.15 - -20.09]	14.78 [8.97 - 19.77]	0.43 [0.35 - 0.50]

Figures 5.7, 5.8, and 5.9 shows a scatter plot of range90 of $AUCEdrs$ and tidal volume Vt with an example model fit for a breath and its corresponding $Edrs$ curve. Patient 15 had the best correlation, Patient 11 had moderate correlation and Patient 22 had poor correlation. The example model fit curves within these figures show how Edrs is able to capture the rest of the observed breathing mechanics. Scatter plots for all patients can be seen in Appendix A.

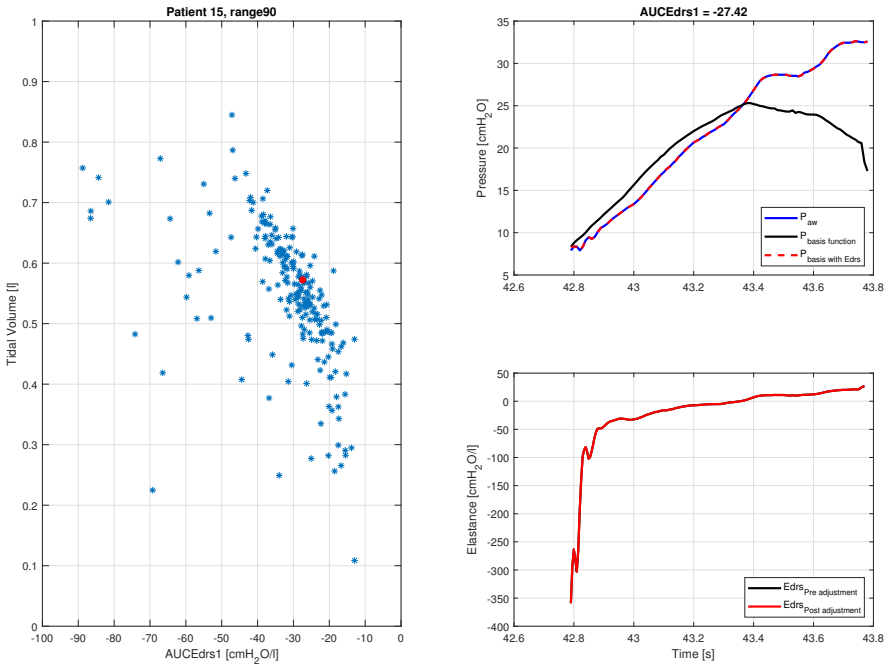

Figure 5.7: Scatter plot with good correlation of $AUCEdrs$ and Vt from Patient 15. The specific breath is red dot.

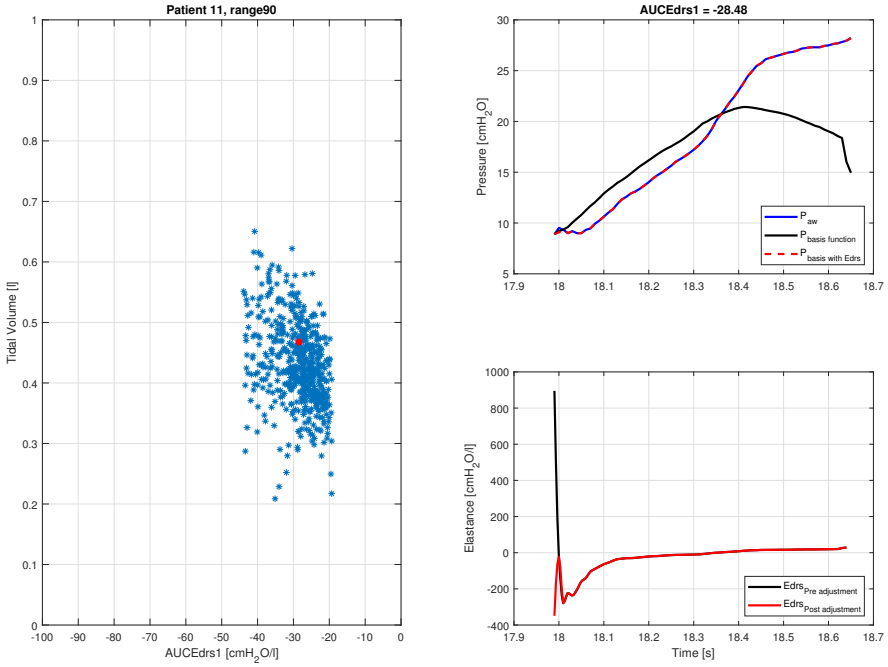

Figure 5.8: Scatter plot with moderate correlation of $AUCEdrs$ and Vt from Patient 11. The specific breath is red dot.

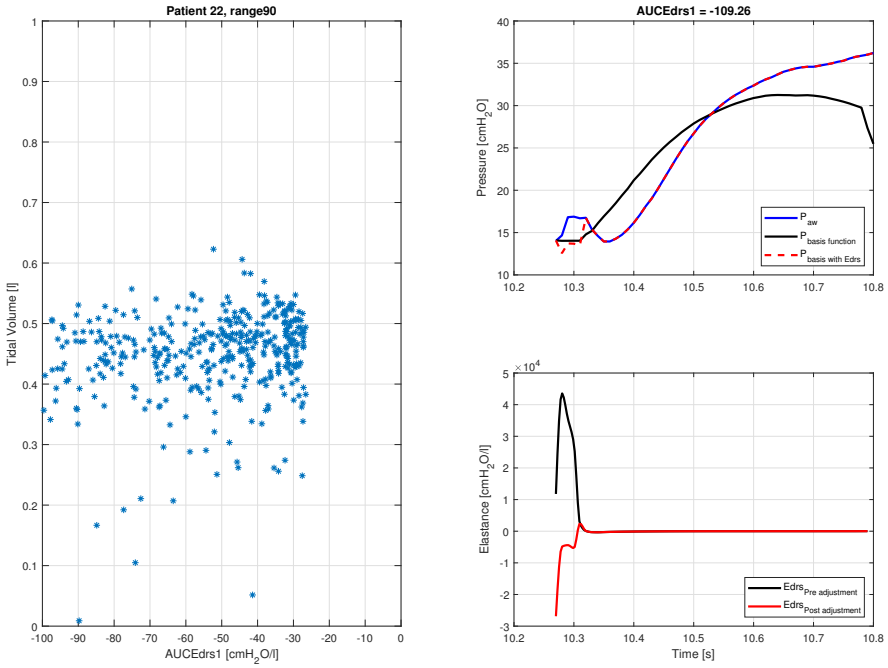

Figure 5.9: Scatter plot with bad correlation of $AUCEdrs$ and Vt from Patient 22. The specific breath is red dot.

5.3.3 Asynchrony

Table 5.2 shows asynchrony detected for each patient. From this table, Patients 4, 8, 16, and 22 have high asynchrony rates. Patient 22 was mostly asynchronous with 70.69%

of breaths displaying asynchrony. Patients 1, 5, 12, and 21 had zero incidence of asynchrony.

Table 5.2: Model Fitting Results

Patient #	Total Breath [N]	Asynchronous Breath [N]	Percentage Asynchronous [%]
1	249	0	0.00
2	615	3	0.49
3	452	3	0.66
4	173	126	72.83
5	749	0	0.00
6	553	105	18.99
7	340	3	0.88
8	300	22	7.33
9	470	49	10.43
10	683	19	2.78
11	616	2	0.32
12	497	0	0.00
13	732	16	2.19
14	334	4	1.20
15	237	5	2.11
16	385	79	20.52
17	706	82	11.61
18	459	5	1.09
19	576	4	0.69
20	434	1	0.23
21	221	0	0.00
22	928	656	70.69

5.4 Discussion

The recruitment basis function used in this chapter, has previously been used and validated in sedated adults on conventional fully supported mechanical ventilation modes. E_1 has been utilised to identify patient alveoli recruitment (Morton et al., 2018, 2019b,a). The time-varying elastance model also used in this chapter, captures patient effort through

the use of dynamic elastance, $Edrs$ (Chiew et al., 2015a). These two models were utilised in a two-step approach to capture patient lung condition in partial ventilation cohort, in attempt to further quantify patient effort. Overall, $E1$ was able to capture patient-specific lung condition and $Edrs$ was able to capture patient effort through $AUCEdrs$.

The overall identified E_1 in this cohort was 46.14 [27.38 - 71.85] cmH_2O/l and the quantified spontaneous breathing effort, $AUCEdrs$ was -33.49 [-52.15 - -20.09] cmH_2O/l. There was large variation in both E_1 and $AUCEdrs$ across the patients as seen in Table 5.1. These results match value and inter-patient variability seen in Morton et al. (2019b,a). Patient 19 had the largest E_1 median [IQR] range with 99.27 [87.69 - 109.50]cmH_2O/l, and low tidal volumes of 0.29 [0.24 - 0.34]l. Similarly Patient 15 had E_1 of 90.37 [77.30 - 107.92]cmH_2O/l with median tidal volume ranges of 0.54 [0.47 - 0.61]. These higher elastance values suggest, these two patients have much stiffer lungs compared to other patients.

The E_1 value cannot be fully fit to inspiration of NAVA cohort clearly showing there are un-modelled, non-passive patient dynamics in the data. This is largely due to the fact the basis function best reflects fully controlled ventilation in sedated patients, where patient breathing is driven by the ventilator and pressure outcomes are a function of recruitment and airway resistance only. In addition, many ventilator supported breaths are either ramped or square in shape, whereas NAVA breaths are more linear, as a result of the NAVA mode and these dynamics.

Figure 5.10 shows example breath with inspiratory pressure, model fits, $Edrs$ and Eadi for Patient 21. In this figure, the basis function model fit towards the end of the breath appears to have poor fit. However, given the maximum volume reached, only small positive Edrs is required to compensate for this apparent error and therefore the model fitting using basis function is acceptable. Physiologically, this difference occurs as pa-

tient effort is ending, the air is forced in by the ventilator and thus, positive $Edrs$ is seen, which is much like the always positive $Edrs$ seen in fully sedated passive ventilation.

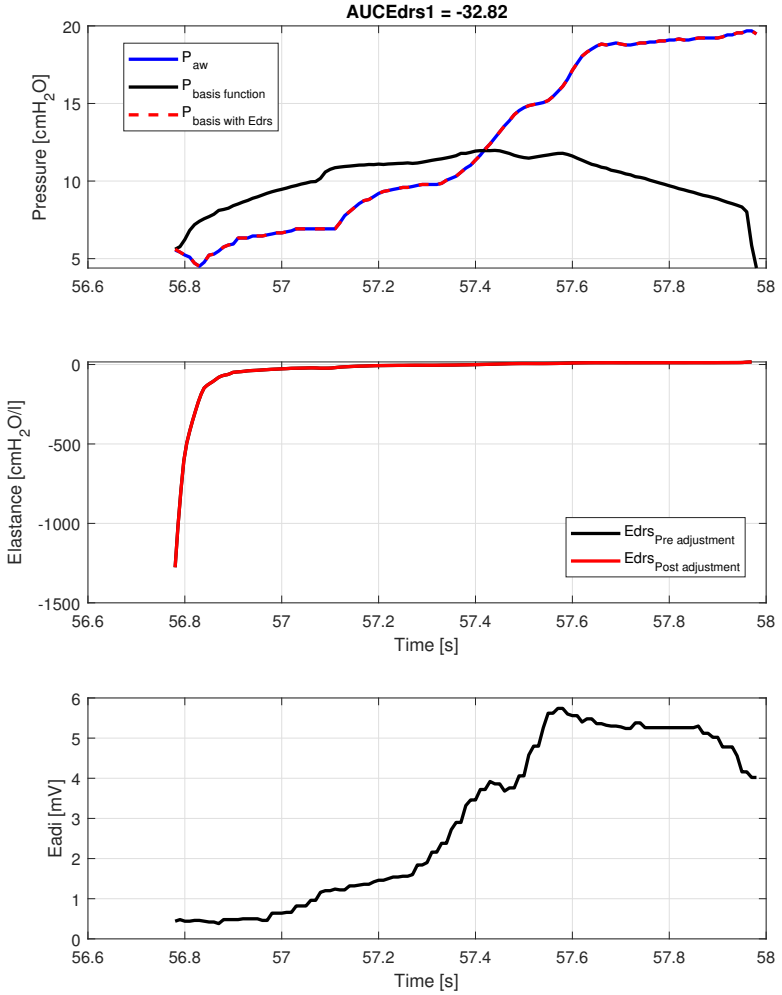

Figure 5.10: Example Pressure with model fit, $Edrs$ and Eadi.

Figures 5.7, 5.8, and 5.9 showed good, typical and poor correlation between patient effort and tidal volume delivered. Patient 15 and 11 shows good and moderate correlations, clearly showing a linear trend. This trend shows the lower the tidal volume delivered, lower the spontaneous breathing effort. This outcome matches the method used by the NAVA mode, as tidal volume is adjusted based on the diaphragm activity of the patient meaning higher the activity (higher demand), more volume is delivered and Figures 5.7 and 5.8 definitely shows this trend. Patient 22 from Figure 5.9 does not show same linear trend as other patients. Notably, poor correlation was only seen in 4 patients of the 22

analysed. Most were good (see Appendix A).

Figures 5.11, 5.12, and 5.13 shows scatter plots comparing $AUCEdrs$ with $Eadi$ for the same three Patients 11,15, and 22. The $AUCEdrs$ trend with $Eadi$ is similar to Vt as expected. Moorhead et al. (2013) showed the Eadi and Vt have linear correlation and thus the when both are compared with AUCEdrs is expected to show similar trends (Moorhead et al., 2013). Intuitively, the Eadi measures electrical activity of diaphragm to control patient breathing and therefore should be correlated with tidal volume as higher diaphragm movement indicates larger breath is needed and thus larger tidal volume is supplied. The figures comparing AUCEdrs with Vt and Eadi showed same trends, which implies the $AUCEdrs$ is a metric that can be used to measure spontaneous breathing effort without the use of external and/or invasive sensors as required with NAVA.

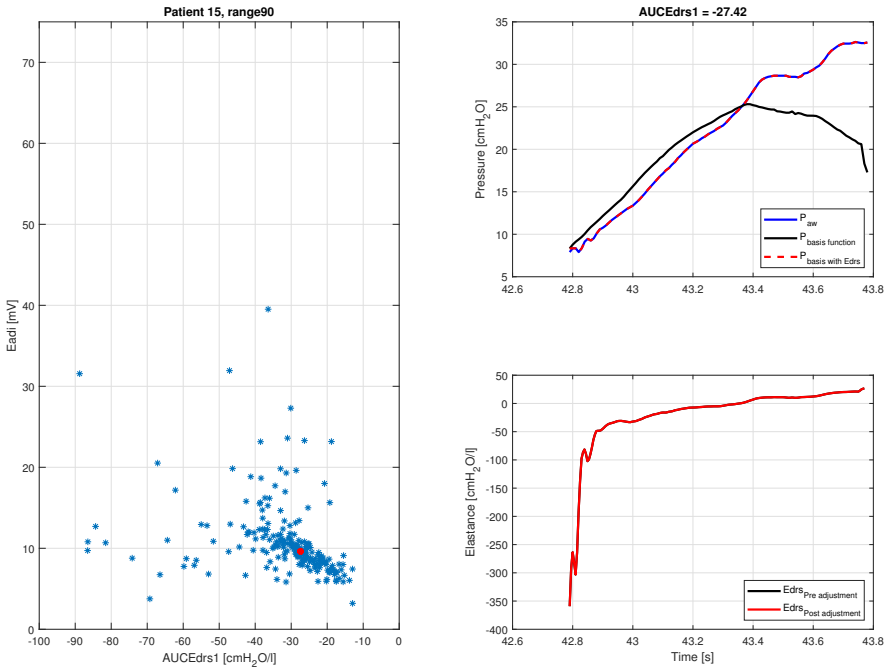

Figure 5.11: Scatter plot with good correlation of $AUCEdrs$ and Vt from Patient 15.

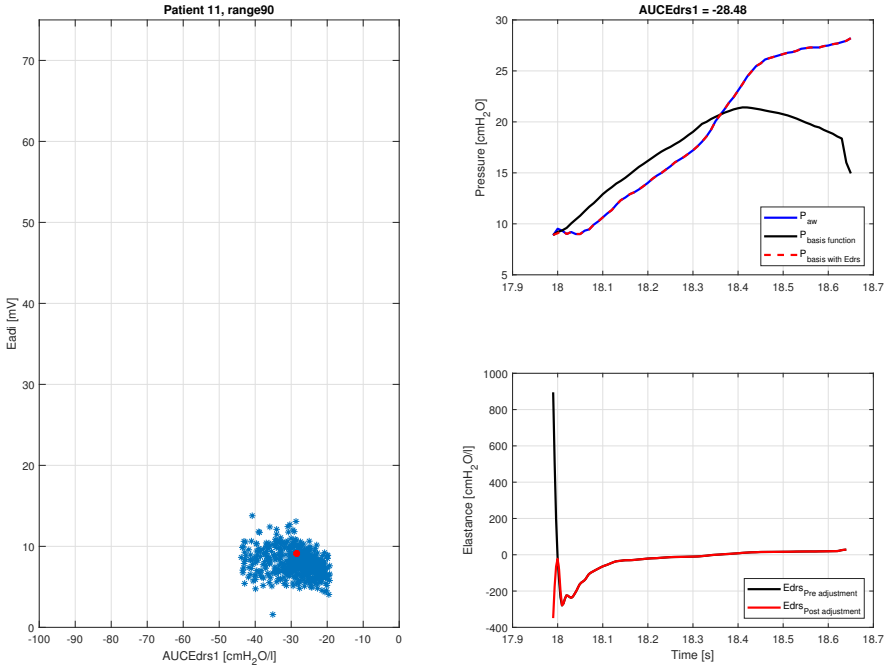

Figure 5.12: Scatter plot with moderate correlation of $AUCEdrs$ and Vt from Patient 15.

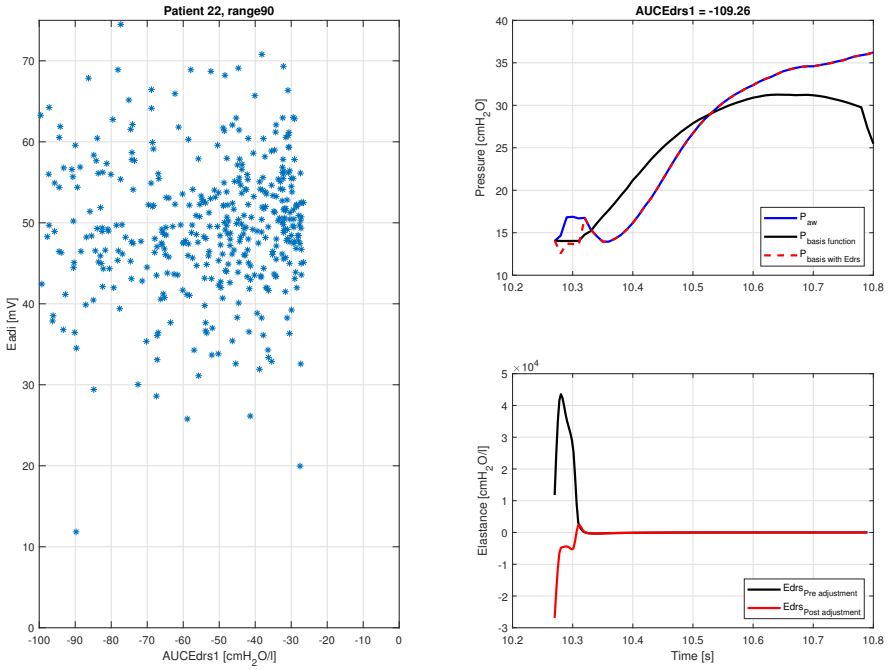

Figure 5.13: Scatter plot with bad correlation of $AUCEdrs$ and Vt from Patient 15.

The poor correlation between $AUCEdrs$ and Vt is an indication of large patient-ventilator asynchrony present. Table 5.2 shows asynchrony rates of each patient and high incidence of asynchrony matched Patients with poor corellations between $AUCEdrs$ and Vt. $Edrs$ used in this analyses captures patient effort from very early portion of inspi-

ration. In this analyses, the early positive $Edrs$ is also adjusted due to fluctuations that occur in normal NAVA breathing. However, doing so on asynchronous breath, results in altering of 'correct' $Edrs$ behaviour.

Top Figure 5.14 shows boxplot of AUCEdrs values for all patients and bottom shows AUCEdrs values after asynchronous breaths has been removed. Patients who had more asynchronous breaths such as Patients 6 and 22, the AUCEdrs is less variable and their interquartile range is much narrower. This indicates some of the patients were highly asynchronous during their recording period and thus, can not truly represent their spontaneous breathing effort in which results in poorer correlation between patient effort and tidal volume seen in Appendix 1.

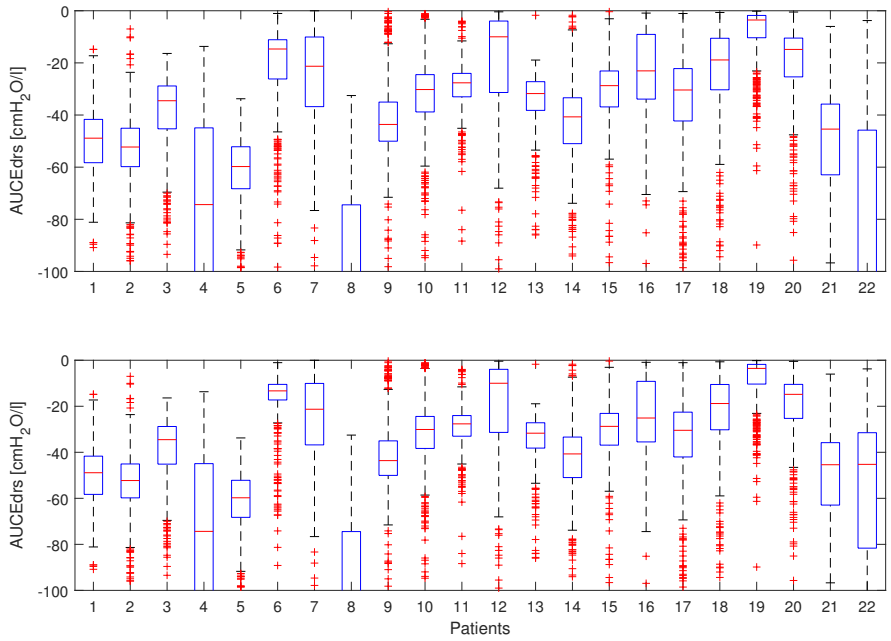

Figure 5.14: Boxplot of AUCEdrs per patient. Top) All patient breaths. Bottom) Asynchronous breaths removed.

Further study will be required to apply this method to capture patient-spontaneous breathing effort in clinical environment. Although this model was able to capture both patient-specific lung mechanics, condition and patient effort, further validation will be required.

5.5 Summary

Overall, the basis function with time-varying elastance model was able to capture both patient-specific elastance and spontaneous breathing efforts. The E_1 was fit to the data from 30% to 70% inspiration due to large spontaneous breathing effort occurring early in the inspiration. $AUCEdrs$ was able to accurately quantify patient effort in comparison to tidal volume with good correlation or better for 18 of 22 subjects and captured expected trends well.

CHAPTER 6

Clinical Utilisation of Respiratory Elastance

6.1 Introduction

It is well known and established to use lower tidal volumes in MV therapies (Brower et al., 2004). However, there is relatively no consensus for PEEP selection (Briel et al., 2010; Oba et al., 2009; Mercat et al., 2008b; Meade et al., 2008; Villar et al., 2006; Amato et al., 1998; Brower et al., 2004; Major et al., 2018). Traditionally, lower PEEP have been used to minimise risk (Gattinoni et al., 2003; Hickling et al., 1990), but low PEEP can lead to increased cases of oxygen desaturation and hypoxaemia (Guerin, 2011; Brower et al., 2004) and worsened lung injury indicated by a greater number of rescue therapies and death after rescue therapy (Briel et al., 2010). High PEEP is able to increase alveoli recruitment, but can decrease cardiac output and lead to further lung injury by barotrauma and/or volutrauma or overdistension (Hillman and Albin, 1986; Petersen and Baier, 1983; Gammon et al., 1992; Cullen and Caldera, 1979; Thammanomai et al., 2013;

Dreyfuss and Saumon, 1992; Briel et al., 2010; Brower et al., 2004; Albaiceta and Blanch, 2011; Tremblay and Slutsky, 2006; Slutsky and Ranieri, 2013b).

PEEP can be optimised to reduce hypoxemia (Meade et al., 2008) and intrapulmonary shunting (Mercat et al., 2008b), improve gas exchange (Oba et al., 2009) and oxygenation (Brower et al., 2004; Borges et al., 2006; de Matos et al., 2012), by maintaining recruitment of injured or collapsed alveoli (Thammanomai et al., 2013). In patients with ARDS, lower PEEP reduces ventilator-induced lung injury (VILI) (Briel et al., 2010; Brower et al., 2004; Albaiceta and Blanch, 2011; Tremblay and Slutsky, 2006; Slutsky and Ranieri, 2013b), increases recruitment (Malbouisson et al., 2001; de Matos et al., 2012; Borges et al., 2006), and reduces inflammatory mediators in plasma and bronchoalveolar lavage fluid (Oba et al., 2009). It has been hypothesized MV strategies combining low tidal volumes with recruitment manoeuvres (RMs) and higher PEEP to prevent VILI would be ideal for lung protection (Rose et al., 2009; Meade et al., 2008). However, currently, there is still no standardisation of how this potentially higher optimal PEEP should be selected, nor how often it should be adjusted or recalculated.

Experimental animal trials by Lambermont et al. (2008); Suarez-Sipmann et al. (2007); Carvalho et al. (2007) (Lambermont et al., 2008; Suarez-Sipmann et al., 2007; Carvalho et al., 2007) reported ARDS induced pigs experienced a minimal respiratory elastance at a specific PEEP associated with higher oxygenation, maximum recruitment, and higher functional residual capacity, all without signs of lung overdistension. Equally, it has been proposed to set PEEP where the lung has minimal respiratory elastance (or maximum compliance), which could be clinically beneficial by balancing the risks of PEEP set too low or too high (Suter et al., 1975; Chiew et al., 2015c; Pintado et al., 2013). Aside from the work by Suter et al. (1975) (Suter et al., 1975), Pintado et al. (2013) (Pintado et al., 2013) also showed PEEP selection at minimal elastance is beneficial to patients. Despite some consistent findings, the application of minimal elastance PEEP selection

remains limited and hindered by the lack of an objective, reliable, and easy to use this method to determine elastance at the bedside in real time.

In a pilot study, Chiew et al. showed the potential benefit of minimal-elastance PEEP selection (Chiew et al., 2011, 2015c). Following the study, a phase 2 randomised controlled trial (RCT) was designed to assess mechanical ventilation of ARDS patients at minimal elastance PEEP versus standard practice of care in a single centre hospital. In particular, patient-specific respiratory system elastance and corresponding minimal elastance PEEP is determined using a validated model-based method and computer software (Szlavecz et al., 2014). This trial uses real-time identified patient-specific respiratory system elastance, and thus the trial is named Clinical Utilisation of Respiratory Elastance (CURE) RCT. This manuscript presents the detailed clinical protocol for this phase 2 CURE RCT. This trial is registered with the Australian New Zealand Clinical Trial Registry (ANZCTR): ACTRN12613001006730

The CURE trial was initially proposed in 2014. Since then, the protocol for this trial has gone through extensive and significant changes. These changes were applied to make this trial more pragmatic, and safe. The Acute Respiratory Distress Trial (ART) (Cavalcanti and ART Investigators, 2017) raised concerns with the use of recruitment manoeuvre as this study resulted in higher mortality and length of stay. Therefore significant changes have been made to the trial design. In this chapter, the protocol for CURE trial is presented in full, outlining and presenting all the details required for any such clinical trial (Kim et al., 2020).

6.2 Methods

6.2.1 Methods and Trial Design

The CURE RCT is a two-arm randomised controlled trial comparing model-based mechanical ventilation (MBV) with current standard practice mechanical ventilation (SPV) in patients with a partial pressure of arterial blood oxygen (PaO_2) / fraction of inspired oxygen, (FiO_2), P/F ratio ≤ 200. It is to be conducted in a single centre hospital intensive care unit (ICU), Christchurch Hospital, in Christchurch, New Zealand.

The primary objective is to assess the impact of model-based ventilation in PEEP selection (MBV) therapy on clinically significant patient outcomes and patient centred quality of care metrics. The other objectives of this study include: 1) to provide the knowledge and methods to make care more patient-specific and timely to optimise treatment and improve outcomes for a large cohort critically ill patients; and 2) to improve the understanding of the patho-physiological basis of critical illness via what we will learn about the hourly and daily evolution of lung injury in terms of patient-specific elastance and response to care through this study.

The primary outcome of this study is the area under the curve (AUC) of PaO_2/FiO_2 over the period of mechanical ventilation. Secondary outcomes include: length of MV (LoMV), ventilator free days (VFD) up to 28 days, ICU and hospital length of stay (LoS), AUC of SpO_2 / FiO_2 during MV, number of desaturation events (frequency and fraction of time $SpO_2 < 88\%$), changes in respiratory mechanics and chest X-ray Index scores, rescue therapies (prone positioning, nitric oxide use, ECMO) and hospital and 90-day mortality. These outcomes and their corresponding four levels of specification based on Zarin et al. (2011) are shown in Table 6.1. The secondary analysis includes comparison of the means of: length of MV, VFD, length of stay of hospital and ICU, 90 day mortality, chest

Table 6.1: Four levels of specification in primary and secondary outcomes

Level 1: Domain	Level 2: Specific Domain	Level 3: Specific Metric	Level 4: Method of Aggregation
Oxygenation	AUC P\F ratio	Difference in AUC	Comparison of the means of AUC
	AUC SpO_2/FiO_2		
MV	Length of MV	Number of Days	Comparison of the means of number of days
	Ventilator Free Days (VFD) up to 28 days	28 days - days of MV	Comparisons of the means of VFD
Length of Stay	Hospital	Number of days	Comparisons of the means of length of stay
	ICU		
	90-day mortality	Time to event	Comparison of number of 90 day mortality
Other	Chest X-ray index scores	Index scores over period of MV	Comparison of index scores over time
	Rescue therapies	Comparisons of index scores over time	Comparisons of rescue therapies used

x-ray index scores, and rescue therapies used.

A difference in primary and secondary outcomes will show the impact of MBV compared to SPV. No difference would show that enhanced, model-based metrics of patient-specific condition have no effect on patient-centred or clinical outcomes. Either outcome will yield clinical guidance.

Two Arm Randomised Controlled Trial

Eligible patients are randomised to either the model-based intervention group (MBV) or the control group (SPV). Both groups will have designated computer software to monitor their breathing (Szlavecz et al., 2014). The software uses real-time measurements of pressure and flow from the ventilator to objectively calculate the patient- and breath-specific respiratory system elastance for every breath (Szlavecz et al., 2014).

Participants on MBV will undergo recruitment manoeuvres (RM), an initial maximum recruitment manoeuvre (RM_{Max}) or subsequent PEEP adjUstment and Monitoring Procedure (PUMP) mini recruitment manoeuvres. The respiratory elastance at each PEEP step during these protocolised RMs is calculated and recorded. The software will recommend a patient-specific minimal-elastance PEEP to the clinicians in setting ventilator PEEP. Patients on SPV will have PEEP selected using current clinical practice without the aid of the software, but all breaths will be analysed and elastance recorded blind to clinical staff

Adherence to intervention

Patients recruited into this study will be under constant supervision in the ICU. However their outcomes are measured by intent to treat, taking into account protocol variations, which naturally occur. These variations will be reported to primary investigator at the earliest opportunity and followed up. There will be detailed training on the use of CURE equipment and protocol to allow adherence to trial.

Protocol amendments

This trial is based on intention to treat. Thus, protocol amendments may be required to ensure patient safety and outcomes, and the primary investigators will instigate protocol amendments if necessary. The amendments will be reviewed by the data monitoring committee (DMC) to warrant patient safety and outcomes. The DMC may also refer protocol amendments based on outcomes of the interim analysis reports. Finally, if participant enrolment is slow, amendments may also be made to allow faster recruitment.

Concomitant care and intervention

The trial results critically ill participants who are mechanically ventilated. Thus, it is likely and acceptable for participants to be receiving medication related to any other concomitant co-morbid conditions while participating in CURE RCT.

Participants of this study will not be concomitant to another study that would affect the results of this study. Participants will not be co-enrolled to another study that have different oxygenation settings, recruitment manoeuvre procedures and anything that may affect the outcomes of this study.

6.2.2 Eligibility Criteria

The following are the CURE RCT inclusion, exclusion and P/F ratio criteria:

Inclusion Criteria

1. P/F ratio $\leq$ 200
   - i on any level of PEEP or FiO_2, OR
   - ii P/F ratio $\leq$ 200 on FiO_2 = 50% and PEEP = 5

Exclusion Criteria

1. P/F ratio $>$ 300 on any level of PEEP or FiO_2
2. P/F ratio $>$ 200 on FiO_2 = 50% and PEEP = 5
3. Ventilated $>$ 48 hours (including time spent in another hospital)
4. Not expected to be ventilated for another 48 hours
5. Patients with age $<$ 16.
6. Any medical condition associated with a clinical suspicion of raised intracranial pressure and/or a measured intracranial pressure $\geq$ 20 mmHg.
7. Patients who have a high spinal cord injury with loss of motor function and/or have significant weakness from any neurological disease.
8. Patients who have a barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema or any intercostal catheter for the treatment of air leak).
9. Patients who have asthma as the primary presenting condition or a history of significant chronic obstructive pulmonary disease.
10. Patients who are moribund and/or not expected to survive for $>$ 72 hours.
11. Agreed limitations of care due to co-morbidities, or not expected to survive 90 days
12. Lack of clinical equipoise by intensive care unit (ICU) medical staff managing the patient. (For example, patients with unremarkable CXR findings with possibility of thrombotic or fat pulmonary emboli).
13. Patients previously been enrolled in CURE RCT

P/F ratio Criteria

1. P/F ratio $\leq$ 200; Patient is eligible for enrolment

2. If 200 $<$ P/F ratio $\leq$ 300; Set FiO_2 = 50% and PEEP = 5 cmH_2O and repeat the ABG within 10 minutes of the change to measure the new P/F ratio:
   (a) If the new P/F ratio $\leq$ 200; Patient is eligible for enrolment.
   (b) If the new P/F ratio $>$ 200; Patient is not eligible for enrolment and, if appropriate, will be re-screened at later time.

This trial will recruit patients who have P/F ratio $\leq$ 200, a criterion in the definition of severe to moderate ARDS defined by The ARDS Definition Task Force- The Berlin Definition (Definition et al., 2012). They will be eligible if their P/F ratio is $\leq$ 200 on any level of PEEP and FiO_2. Those patients with a 200 $<$ P/F ratio $\leq$ 300 will be placed on PEEP = 5 cmH_2O, and an FiO_2 = 50%. If a subsequent P/F ratio is $\leq$ 200 they will also become eligible. The P/F ratio measured at FiO_2 of 50% and PEEP of 5 cmH_2O is based on Villar et al. 2013 (Villar et al., 2013).

6.2.3 Consent,compliance, and withdrawal

Consent Procedure

First, it is important to note standard ventilation practice may include recruitment manoeuvres to increase lung recruitment and oxygenation. However, these clinical practices are widely variable and often not standardised. The recruitment techniques used to improve oxygenation and mechanics of ventilation in the intervention and control arms of this study are within the scope of standard ICU clinical practice. The protocols used will standardise these existing interventions to recruit lung volume and titrate PEEP.

Study participants will be unable to consent to participation in this study prior to enrolment as they will be sedated and mechanically ventilated. It is also equally important participants be randomised into either arm of the RCT at the commencement of MV to ensure a fair comparison. Patients who have been ventilated $\leq$ 48 hours are eligible for

the CURE RCT. Given this time frame, CURE RCT will recruit patients once family consent is obtained. However, if the treating clinician firmly believes a recruitment manoeuvre is in the best interests of the patient, and no family is available for consent, the participant will be enrolled and randomised and the appropriate protocolised recruitment manoeuvre will follow. In this case, delayed consent is obtained as early as possible. Once the participant recovers from their condition and is discharged from the ICU, we will seek their informed consent.

In cases where the family cannot attend the hospital to sign a statement of assent, their opinion will be obtained by telephone in the first instance. Information about the study will either be made available by emailing them the information sheet and contacting them later by telephone, or the information sheet will be read to them over the telephone. The telephone conversation(s) and their opinions will be documented in the patient's medical record. As soon as the family is able to attend the hospital, they will be asked to sign the statement. If the family are not able to sign a statement during the patient's time in the ICU, they have the option of printing out the statement, signing it, and mailing/emailing/faxing it back.

Withdrawal of consent

If the participant's family / relative/ friend do not agree to their continued participation, they will be withdrawn from the study and we will seek agreement from them to use information related to mechanical ventilation collected up until that point.

If a participant chooses to withdraw from the trial, we also will seek agreement to use information related to mechanical ventilation collected up until that point. If they do not agree, then all study information obtained will be destroyed.

Randomisation and Blinding

Randomisation will be performed in blocks, where the block sizes are generated using a randomisation program. The program will randomly assign patients into either a control group or intervention group through a random block size (block size is either 4, 6, 8 or 10 patients). Eligible and consented patients will be block randomised with a ratio of 1:1. No effort will be given to stratifying the subgroups considered in the secondary analyses. By the nature of the intervention, CURE cannot be double-blinded. Un-blinding is not applicable due to the nature and setting of the intervention.

6.2.4 Ventilation settings, Oxygenation, and Patient Positioning

Tidal volume and driving pressures during MV

Tidal volume (V_T) is adjusted to 6-8 ml/kg per ideal body weight (IBW), and the maximum minute ventilation (V_{Emax}) $\leq$ 0.2 L/kg/minute. The ideal body weight (IBW) is measured by the patient's height and look-up table at the bedside or calculated using the formulae:

$$Men : 50 + 0.91 \times (height[cm] - 152.4)kg \tag{6.1}$$

$$Women : 45.5 + 0.91 \times (height[cm] - 152.4)kg \tag{6.2}$$

The driving pressure (DP) is the plateau pressure (P_{Plat}) minus the PEEP. In patients with very severe ARDS 6-8 ml/kg may be injurious if the DP is higher than 15 cmH_2O. A DP $\leq$ 15 cmH_2O was associated with better patient survival when assessed using a multilevel mediation analysis of 3562 patients in 9 RCTs of ARDS (Brochard et al., 2015). Therefore, the DP will be limited to $\leq$ 15 cmH_2O at all times. In addition, during spontaneous ventilation, pressure support will be limited to $\leq$ 15 cmH_2O.

Ventilation rate is set between 12 and 20 breaths per minute. The aim is to keep the plateau pressure $P_{plat} \leq$ 30 cmH_2O. If necessary, V_T may be reduced as low as 4 ml/kg

and the respiratory rate (RR) kept $\leq$ 30 breaths per minute. CO_2 will frequently rise in severe lung injury (permissive hypercapnia) when patients are mechanically ventilated within these guidelines. However, if $CO_2 \geq 80$ mmHg or increased $\geq 50\%$ in the previous 4 hours, the intensive care specialist on duty will be notified, and they may choose to deviate from these guidelines.

Ventilation Mode

All patients enrolled are to be ventilated using a pressure-controlled mode. For example, the Bi-Level ventilation mode on the Puritan Bennett PB840 ventilator (Covidien, Boulder, CO, USA), or PC-SIMV+ on the Drager Evita Infinity V500. Patients will be ventilated using Bi-Level/PC-SIMV+ mode, which allows unrestricted spontaneous breathing efforts to lessen ventilator dyssynchrony. However, during any recruitment manoeuvre procedures, synchronized intermittent mandatory ventilation (SIMV) with pressure-controlled (PC) ventilation is used and returned to original mode afterwards. Should patients already be ventilated using a ventilator incompatible with the CURE computer system, they will have their ventilator changed to a compatible ventilator for the trial. Patients will be transitioned to Assisted Spontaneous Breathing (ASB) if they meet the weaning criteria.

In severe ventilator dyssynchrony, a very a high respiratory drive may result in sub atmospheric circuit pressures and risk of aspiration of gastric contents around the endotracheal cuff. If a participant has a high respiratory drive on Bi-Level/PC-SIMV+ ventilation, producing a fall in airway pressure during inspiration, muscle relaxants will be considered to facilitate controlled breathing. However, if the clinician feels the participant may benefit from breathing spontaneously, transition to ASB may be made if they substantially meet the weaning criteria.

However, spontaneous breathing efforts may mask high trans-pleural pressures and

produce high levels of regional lung strain. Oesophageal pressures will not be measured during this trail. If the treating clinician is concerned about patient self-inflicted lung injury (P-SILI) (Brochard et al., 2017; Brochard, 2017), they will consider using muscle relaxants to control ventilation.

Patients will not undergo any procedures using a cough assist machine prior to weaning and transitioning to spontaneous breathing. However, the treating clinician may use a cough assist machine to aid secretion removal (during spontaneous breathing) if they believe it is in the patient's best interests.

Finally, in any circumstances where the patient is planned to be temporarily disconnected from the ventilator, their endotracheal tube will be clamped to prevent de-recruitment

SpO_2 Targets

To ensure a fair comparison, all CURE study participants will have inspired oxygen levels titrated to achieve the following pulse oximetry saturations, SpO_2:

i) SpO_2 = 93-95% if FiO_2 is less than 60%.
ii) SpO_2 = 90-92% if FiO_2 is greater than or equal to 60%.

The aim is to spend greater than or equal to 90% of time in the target range. The FiO_2 should only be increased above 21% if these targets are not met, using 5% increments starting with a FiO_2 = 25%. There is natural variability in SpO_2 levels. To avoid toggling between two FiO_2 levels, 10 minutes of settling time will be allowed before changing the FiO_2. The best FiO_2 is chosen to keep the saturation over 90% of the time within the specified targets ranges.

Patient Position, Turning, and Prone Positioning

Patients are kept at 30° head up whenever possible. This position maximises recruitment of the lung and may reduce the risk of aspiration. Wherever possible, patients should be rolled from supine to right-side down, back to supine, then to left-side down. This turning of patients is ideally performed every 3 hours.

Transient hypoxaemia frequently occurs after a patient has been turned and may be worse if there is inadequate PEEP. Hypoxaemia may also become more severe if participants are rolled from left-side down to right-side down due to cyclical de-recruitment of the non-dependent lung and re-recruitment of the dependent lung. This cyclical de-recruitment of the lung has the potential to contribute to VILI. Thus, patients with severe lung injury may be very intolerant of being turned. In some instances, the lungs may need to be re-recruited. If desaturation does occur, this will be recorded as a serious adverse event (SAE).

Prone positioning of patients may be considered if the P/F ratio is ≤ 100 and $FiO_2 \geq 60\%$. Patients randomised to the intervention arm (MBV) may still undergo a protocolised recruitment manoeuvre. For patients in the standard practice ventilation arm (SPV) a staircase recruitment manoeuvre is left to clinical judgement.

6.2.5 Arterial blood gas (ABG) recordings

The primary outcome of this trial is the AUC of the P/F ratio. For this reason, mandatory daily ABGs are performed daily for up to 10 days from enrolment. ABGs are taken around 0600 hours and 1800 hours. The ABGs are also acquired within 60 minutes of any recruitment manoeuvre procedure and 30-60 minutes after the recruitment manoeuvre procedure. The added ABGs from RM procedures will be used in secondary analysis, but will be omitted during primary analysis to ensure the same number of data points per day for all patients.

6.2.6 Duration of intervention

Patients randomised to the model-based ventilation (MBV) cohort will remain in the protocol up to 10 days. Thereafter, they will receive the same care as participants assigned to standard practice ventilation (SPV). However, if participants have been extubated, but then require intubation and re-ventilation at any time within 10 days of enrolment, they will return to the original assigned protocol (MBV or SPV). All patients will receive standard care beyond 10 days of enrolment, and their data recording including ABG recordings will continue to be collected for up to 28 days.

6.2.7 General Procedures

Procedures for Control group, SPV

1. PEEP is selected as per standard practice.
2. The decision to carry out a staircase recruitment manoeuvre will be based on clinical judgement. The protocol for performing staircase recruitment manoeuvre is explained in the recruitment manoeuvre section.
3. ABGs will be taken twice daily.
4. Ventilator data collected continuously until disconnected.

Procedures for Intervention group, MBV

1. For patients included for MBV (intervention), the PEEP and MV will be guided by clinicians using bedside computers while maintaining V_T and FiO_2.
2. Patients randomised to MBV will undergo protocolised recruitment manoeuvres (RM)
   (i) Before the RM, the patient should be sedated and paralysed, if required, with muscle relaxants to prevent spontaneous breathing efforts.
   (ii) The first RM used is a Maximum Recruitment Manoeuvre (RM_{Max}). This is done at the beginning of the trial by clinicians and only repeated if clinically

indicated.

(iii) The PEEP adjUstment and Monitoring Procedure is referred to as a 'PUMP', where the PEEP is adjusted -4 cmH_2O to +4 cmH_2O of the current PEEP setting. The PUMP may be performed by ICU staff trained in this technique.

3. The participant will no longer undergo a PUMP when:
   a $FiO_2 \leq 35\%$,
      i And they have fully transitioned to spontaneous breathing
      ii And the, $PaO_2 \geq 60$ mmHg for the last 24 hours, **OR**
   b After 10 days from study enrolment.
   c At the discretion of the clinician, for example:
      i New neurological condition
      ii They are awake and breathing normally without evidence of respiratory distress, and where sedation (with or without paralysis) is not considered to be in their best interests.
4. ABGs will be taken twice daily, and before and after any recruitment procedure.
5. Data will be collected continuously until the patient is disconnected from the ventilator.

6.3 Recruitment Manoeuvres (RM)

Patients enrolled in this study will undergo recruitment manoeuvres. RMs are only carried out by senior medical staff or senior trainees familiar with this technique. Maximum Recruitment (RM_{Max}) and PEEP adjUstment and Monitoring Procedures (PUMPs) are for participants randomised to the MBV protocol arm only. Patients assigned to the SPV arm may undergo a staircase recruitment manoeuvre (SRM) at the discretion of the treating clinician according to standard practice.

All RMs will be performed in SIMV Pressure Controlled (PC) ventilation mode. The peak inspiratory pressure (Pi) is set to achieve a tidal volume (V_T) 6-8 ml/kg IBW. Preferably,

V_T should result in a driving pressure (DP) $\leq$ 15 cmH_2O above PEEP.

Before and after each RM, arterial blood gases (pH, $PaCO_2$, PaO_2, HCO3), SpO_2, end tidal carbon dioxide partial pressure ($ETCO_2$), FiO_2, PEEP, respiratory rate (RR), and V_T will be recorded. In addition, during the RM_{Max} (Model Based Ventilation arm) or SRM (Standard Practice Ventilation Arm), at each PEEP increment, Heart Rate, Rhythm, mean arterial pressure (MAP), SpO_2, FiO_2, V_T, RR, $ETCO_2$, and rates of vasoactive drugs will be recorded. This data will be valuable in assessing the safety of the RM_{Max}, PUMP, and SRM.

In many cases, where the lung stiffness, or respiratory elastance (E) is high, it will not be possible to deliver a V_T of 6 ml/kg. Furthermore, during the recruitment manoeuvre, the delivered V_T may fall further as the elastance increases. As a result, it may be necessary to increase the respiratory rate to accommodate the reduction in minute ventilation. For example, if E is $>$ 40 cmH_2O /L (or compliance $<$ 25 ml/cmH_2O) in a 58 kg (IBW) patient, (normal range 15-20 cmH_2O/L), the V_T will be $<$ 6 ml /kg ($<$350 ml) when the driving pressure is 15 cmH_2O.

It is important that oxygenation targets for both arms are carefully followed to ensure a fair comparison between them. The SpO_2 will be kept in the target range prior to any RM. This approach allows small decreases in oxygenation to be detected during the decremental PEEP phase of the recruitment manoeuvre, while also providing a sufficient buffer in the event of significant de-saturation due to ventilation perfusion (V/Q) mismatch. V/Q mismatch increases with higher airway pressures when pulmonary arterial blood is shunted away from the pulmonary capillaries by-passing aerated regions of the lung.

6.3.1 Recruitment Manoeuvre checklist

Before performing any RM, following criteria are considered. Any RM must be delayed until these conditions are corrected:

1. Consider at-risk patient conditions:
    a Haemodynamic instability (e.g. ongoing haemorrhage).
    b Not optimally resuscitated with fluids? (e.g. stable blood pressure, but pulse pressure variation $\leq 12\%$ because of inadequate left ventricular preload). (Only applicable in absence of spontaneous breathing)
    c Evidence of barotrauma since enrolment? If there is new barotrauma, RMs must not be attempted and the participant will be withdrawn from trial. They will continue to be observed and followed up. A serious adverse event (SAE) will be reported.

6.3.2 Recruitment Manoeuvre preparation steps

Once the RM checklist conditions are met, the patient can be prepared for a RM by ensuring:

1. There is a reliable arterial line.
2. The patient is supine; 15-30° head up
3. The endotracheal tube (ETT) cuff is inflated to 45 cmH_2O (RM_{Max} or SRM) or 35-40 cmH_2O (PUMP) to ensure there is no leak at maximum airway pressures. The ETT cuff is deflated to less than 30 cmH_2O at the end of the RM procedures.
4. The peak pressure alarm is set to 45 cmH_2O (RM_{Max}, PUMP, SRM)
5. SpO_2 is in the target range ($FiO_2 < 60\%$: 93-95% or $FiO_2 \geq 60\%$: 90-92%), and an ABG has been taken within the last 60 mins
6. If patient is not on vasoactive drugs, i.v. adrenaline (or other suitable vasoactive

drug) is available in the event of hypotension.

6.3.3 Recruitment Manoeuvre termination

RMs should be terminated if, at any time during the RM, if any of the following changes persist for more than 3 minutes:

1. Desaturation with $SpO_2 < 88\%$
2. New bradycardia (heart rate $<$ 60 beats per minute) or,
3. New tachycardia (heart $>$ 140 beats per minute) or,
4. New arrhythmia leading to (2) or (3) above or,
5. New hypotension (reduction in MAP by 40% or MAP $<$ 60 mmHg).

This RM termination criteria applies to all recruitment manoeuvre procedures in both arm.

6.3.4 Maximum Recruitment Manoeuvre (RM_{Max}; MBV)

The RM_{Max} is a computer-guided staircase recruitment manoeuvre procedure in the MBV intervention arm. This method is designed to safely increase the inspiratory pressure to a maximum airway pressure of 40 to 43 cmH_2O, with driving pressure (DP) limited to 15 cmH_2O, and maximum PEEP limited to 25-28 cmH_2O. The RM_{Max} is guided by the CURE software using a validated model-based method, which estimates elastance to determine the optimal PEEP (Redmond et al., 2014; Chiew et al., 2015c).

The RM_{Max} is carried out by Intensive Care specialists or senior trainees familiar with this technique. This procedure is only carried out during working hours (0800-1800h), but preferably within 4-6 hours of enrolment. However, for patients enrolled overnight, unless there are compelling reasons to carry out an RM_{Max}, this procedure may be delayed till the following morning (0800 hours).

Contra-indicated preconditions to an RM_{Max} are excluded using the RM checklist. If it is safe to proceed, the patient is prepared for the RM_{Max}.

The following instructions are given to the clinician:

1. Adjust oxygenation to meet the target range.
2. Titrate sedation so the patient is not verbally responsive and has loss of their eyelash reflex. Use fentanyl or morphine increments with propofol to provide a 'balanced' deeper sedation level. Give Rocuronium 1.0 -1.5 mg/kg through a reliable i.v.; ensure the line is flushed.
3. Set the ventilator to SIMV-PC (pressure control) mode.
4. Set peak inspiratory pressure (Pi) to 15 cmH_2O above PEEP.
5. Ensure the initial PEEP is $\leq$ 15 cmH_2O.
6. Start Maximum Recruitment on the CURE soft program.
7. Follow the steps of the CURE Soft protocol: During the RM_{Max}, increase PEEP in steps of 4 cmH_2O above the baseline PEEP level until peak airway pressure reaches (Pi) 40-43 cmH_2O or PEEP 25 to 28 cmH_2O. Then reduce PEEP in 4 cmH_2O decrements until the original starting PEEP is reached. Adjust FiO_2 throughout the procedure to keep $SpO_2 \geq 90$
8. Once PEEP has been returned to the initial setting, perform a second RM_{Max} using the same method in 7. The RM_{Max} is carried out twice. During the first RM_{Max} the elastance changes in PEEP level are more variable and therefore less predictable. The non-recruited lung is highly heterogeneous with regions of collapse and consolidation. The first maximal recruitment manoeuvre is used to recruit these derecruited regions. The second manoeuvre is used to estimate optimal PEEP from repeated estimates of elastance changes during decremental PEEP titration.
9. The CURE soft program will recommend an optimal PEEP at the end of the second RM_{Max}. You may either accept this computerised recommendation, or reject it

(with a reason) if you feel the new PEEP level is inappropriate. If rejected, record your reason(s) on the program.

10. Return the patient to the previous ventilation mode.
11. Adjust $V_T \leq$ 6-8 ml/kg IBW. If the plateau pressure is $>$ 30 cmH_2O, adjust the V_T down to 4-6 ml/kg IBW and tolerate permissive hypercapnia. Also ensure that the DP remains $\leq$ 15 cmH_2O. You may increase the respiratory rate up to 30 breaths/min provided there is no significant auto-PEEP causing breath stacking.
12. Reduce the ETT cuff pressure to the previous level and re-set ventilator alarms to previous settings.
13. Take an ABG 30 to 60 mins following the conclusion of the procedure

6.3.5 Repeating Maximum Recruitment Manoeuvre (RM_{Max})

The RM_{Max} may be repeated only when the following conditions are met:

1. If there is a significant change in the participant's condition, e.g. new severe hypoxaemia ($SpO_2 < 90\%$ and $FiO_2 \geq 60\%$; P/F 100)
2. **AND** patient conditions for which lung recruitment is contraindicated are excluded (e.g. endobronchial intubation, mucous plugging, pneumothorax etc).
3. **AND** analgesia and sedation, and patient position have been optimised (Consider small changes to respiratory rate, tidal volume and pressure support, or a rocuronium infusion).
4. **AND** the PEEP adjUstment and Monitoring Procedure (PUMP) fails to improve oxygenation.

6.3.6 PUMP: PEEP adjUstment and Monitoring Procedure

PEEP adjUstment and Monitoring Procedures (PUMPs) are regular mini-recruitment manoeuvres procedure designed to adjust PEEP level based on patient-specific changes in condition. This mini-RM is also guided by CURE software and moves between $\pm$ 4

cmH_2O from current PEEP level. PUMPs should be performed twice daily during normal working hours (0800-1800h) or at any other time if lung de-recruitment is considered to be the likely cause of new desaturation. The inspiratory pressure (Pi) will be left as same as current ventilator settings.

To ensure a PUMP, can be safely carried out, the RM checklist and preparation steps are to be followed. If the checklist preconditions are met, the PUMP may be carried out.

The following instructions are given to the clinician:

1. Titrate sedation so the patient is not verbally responsive and has loss of their eyelash reflex. Use fentanyl or morphine increments with propofol to provide a 'balanced' deeper sedation level. Give Rocuronium 0.5 -1.0 mg / kg through a reliable i.v.; ensure the line is flushed.
2. Set the ventilator to SIMV-PC mode with appropriate settings mentioned above.
3. Reduce the PEEP to 4 cmH_2O less than the current PEEP setting. The CURE software cannot estimate an optimal PEEP that is lower than the current PEEP setting.
4. Start PUMP on the CURE soft program.
5. Follow the steps of the CURE soft PUMP protocol. During PUMP procedure, increase PEEP in two steps of 4 cmH_2O. Then decrease PEEP in two steps of 4 cmH_2O. (You may need to adjust the FiO_2 to keep the $SpO_2 \geq 90$
6. Once you have returned PEEP to starting PEEP level (initial PEEP -4 cmH_2O), perform a second PUMP using the same method in 5.
7. The CURE soft program will recommend a new PEEP at the end of the second PUMP. You may either accept this computerised recommendation, or reject it (with a reason) if you feel the new PEEP level is inappropriate. If rejected, record your reason(s) on the program.
8. Return the patient to the previous ventilation mode.

9. Adjust to $V_T \leq$ 6-8 ml/kg IBW. If the plateau pressure is $>$ 30 cmH_2O, adjust the V_T down to 4-6 ml/kg IBW and tolerate permissive hypercapnia. Also ensure that the DP remains $\leq$ 15 cmH_2O. You may increase the respiratory rate up to 30 breaths/min provided there is no significant auto-PEEP causing breath stacking.
10. Reduce the ETT cuff pressure to the previous level and re-set ventilator alarms to previous settings.
11. Take an ABG 30 to 60 mins following the conclusion of the procedure

6.3.7 Standard practice Staircase Recruitment manoeuvre (SRM)

Participants assigned to standard practice ventilation (SPV) have PEEP determined using clinical judgement, as per local unit standard care. However, if oxygen requirements are high or have recently increased e.g. an $FiO_2 \geq 50\%$ to keep SpO_2 in the target range of 93-95%, the following should be considered if the treating clinician is intending to carry out an SRM:

1. Patient conditions for which lung recruitment are contraindicated are excluded (e.g. endobronchial intubation, mucous plugging, pneumothorax etc).
2. Analgesia and sedation, and patient position have been optimised.
3. Small changes to respiratory rate, tidal volume, pressure support, or neuromuscular blockade to optimise mechanical ventilation

If the oxygenation does not improve with the above interventions, then PEEP may be increased in increments of 2 cmH_2O. If the PEEP is $\geq$ 15 cmH_2O and $FiO_2 \geq 60\%$, (P/F 100) in spite of addressing the above points, a staircase recruitment manoeuvre (SRM) may be considered if the clinician feels this is in the best interests of the patient.

SRM procedure does not utilise CURE software to perform recruitment and therefore the software will not guide the user, nor make any PEEP suggestions. The software will

still record airway pressure and flow through this procedure.

To ensure a SRM, can be safely carried out, the RM checklist and preparation steps are to be followed. If the checklist preconditions are met, the SRM may be carried out: (Note, the SRM procedure does not utilise CURE software to perform recruitment).

The following instructions are given to the clinician:

1. Titrate sedation so the patient is not verbally responsive and has loss of their eyelash reflex. Use fentanyl or morphine increments with propofol to provide a 'balanced' deeper sedation level. Give Rocuronium 1.0 -1.5 mg/kg through a reliable i.v.; ensure the line is flushed.
2. Set the ventilator to SIMV-PC mode.
3. Set peak inspiratory pressure (Pi) to 15 cmH_2O above PEEP.
4. Ensure the initial PEEP is $\leq$ 15 cmH_2O. If PEEP is set $\leq$ 15 cmH_2O, the corresponding plateau pressure will not exceed 30 cmH_2O
5. Increase PEEP in a stepwise manner every minute in steps of 4 cmH_2O to a achieve Pi of 40-43 cmH_2O.
6. Reduce PEEP to 24, and then by decrements of 2 cmH_2O, every two minutes, until the SpO_2 begins to fall by no less than 2% of the maximum observed. Hold PEEP at this level and then increase PEEP to maximum that was previously used for one minute before returning to a PEEP level 2 cmH_2O above the level when the SpO_2 was first noted to have fallen. (The decrements of 2 cmH_2O will allow a PEEP selection between 16 and 24 cmH_2O, which is within the high PEEP protocol from the ARDS Clinical Network study of high vs. low PEEP [4].
7. If there is no desaturation during the decremental phase of the SRM, reduce PEEP to 16 cmH_2O; no further changes in PEEP are required.
8. Return the patient to the previous ventilation mode.

9. Adjust the DP $\leq$ 15 cmH_2O to give a V_T of $\leq$ 6-8 ml/kg IBW. If the plateau pressure is $>$ 30 cmH_2O, adjust the DP so that V_T is to 4-6 ml/kg IBW and tolerate permissive hypercapnia. You may increase the respiratory rate up to 30 breaths/min provided there is no significant auto-PEEP causing breath stacking.
10. Reduce the ETT cuff pressure to the previous level and re-set ventilator alarms to previous settings. Take an ABG 30 to 60 mins following the conclusion of the procedure

6.4 Ventilator Dyssynchrony

Ventilator dyssynchrony occurs when a patient's spontaneous respiratory efforts are not synchronised with the ventilator. This commonly causes agitation and respiratory distress; often described as "fighting the ventilator". Dyssynchrony should be considered in patients with increased respiratory efforts, unexplained agitation, tachycardia, or sweating. Ventilator wave forms can be used to identify dyssynchrony.

In participants assigned to Model-Based Ventilation (MBV), dyssynchrony will often cause large spikes in the elastance recordings. The CUREsoft algorithm does not account for patient breathing efforts and "sees" inspiratory effort as a rapid reduction in lung elastance (Thille et al., 2006; Carlucci et al., 2013; Chiew et al., 2015a; Redmond et al., 2019; Newberry et al., 2016; Kannangara et al., 2016a; Damanhuri et al., 2016). In contrast, coughing, breath-holding, and other dyssynchronous efforts may cause an apparent increase in elastance (de Wit et al., 2009). Figure 6.1 shows an example of ventilator dyssynchrony in a pressure controlled mode. Dyssynchrony may be seen as negative deflections ("M" waves) in the flow-time waveform, as shown in Figure 6.1. In contrast the airway pressure is may only be changed minimally by patient effort.

It is important to exclude reversible mechanical causes that might lead to patient distress and ventilator dyssynchrony. Endobronchial intubation, obstruction of a major

bronchus, or a pneumothorax should be excluded.

Usually ventilator dyssynchrony can be managed by increasing sedation. However, in many cases it may be preferable to use intermittent muscle relaxants to fully control ventilation. It also may be helpful to trial the patient on assisted spontaneous breathing (ASB) to improve ventilation synchrony, if PEEP $\leq$ 10 cmH_2O and the $FiO_2 \leq 40\%$. However, caution should be exercised, lest the patient become exhausted.

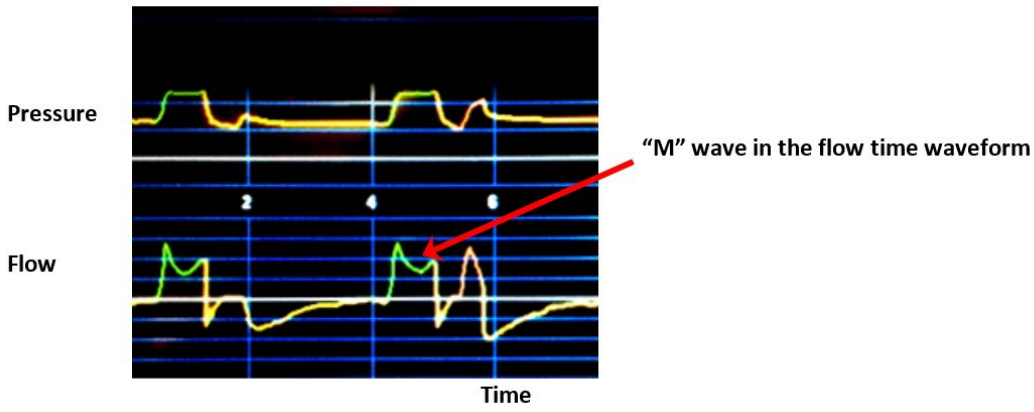

Figure 6.1: An "M" wave is seen in the flow time waveform (flow starvation), followed by a spontaneous (pressure-supported) breath.

6.5 Weaning assessment

These guidelines are a pragmatic and consistent way to transition patients to assisted spontaneous breathing (ASB). Weaning is challenging and difficult to protocolise because there are many different factors to consider. For this reason, the weaning process is typically determined by clinical judgement. However, the guidelines presented here are set to ensure consistency of care.

ASB is considered when the participant's condition is improving. They should preferably be afebrile, have resolution of the underlying processes that led to their ICU admission and improving gas exchange. They should have improving muscle strength, decreasing sedation requirements with an improving Glasgow Coma Score (GCS) and

Richmond Agitation Sedation Score (RASS) between -3 and +1. Generally, the FiO_2 should be $\leq$ 40%and PEEP $\leq$10 cmH_2O.

If the following are substantially present, then participants may be transitioned to ASB:

1. Improving condition
2. Minute ventilation acceptable (VE) $\leq$0.2 L/kg
3. $FiO_2 \leq 40$
4. SpO_2 93-95
5. pH $\geq$ 7.3
6. Heart rate $\leq$ 120/minute
7. Low vasoactive drug requirements (Noradrenaline + adrenaline $\leq$ 10 mcg/minute)

The following instructions or recommendations are used to guide transition to ASB:

1. Set mandatory respiratory rate (RR) $\leq$ 10 cmH_2O
2. Set pressure support (PS) 10-15 cm cmH_2O
3. Consider PEEP level
    a Generally keep PEEP $\leq$ 10 cmH_2O.
    b PEEP maybe up to 15 cmH_2O in obese participants or when the chest wall or abdominal elastance is increased.
4. Monitor RR, HR and SpO_2 over the next 30 mins. If there is significant increase in distress, desaturation, or an increased oxygen requirement, the participant is reverted back to the previous controlled ventilation mode.
5. If there is no significant deterioration, change the ventilation mode to ASB.
6. If the participant is comfortable, you may reduce PEEP and PS after 12 hours. Titrate PEEP and PS as clinically indicated by $\leq$ 2 cmH_2O. PEEP; PS should remain $\geq$ 5 cmH_2O. Reductions in PEEP and PS should be generally made between 0800-

1800h.

Observations during ASB:

1. Check RR, HR and SpO_2 every two hours
   a If there are increases in heart rate, agitation, delirium, respiratory distress, minor desaturations, or an increasing oxygen requirements, ($\Delta FiO_2 \geq 10\%$ or $FiO_2 \geq 50\%$) check the patient and the ventilator:
      i Exclude patient conditions, e.g. endobronchial intubation, mucous plugging, pneumothorax etc.
      ii Optimise analgesia / sedation and patient position
      iii Consider increasing:
         A. Pressure Support up to 15 cm.
         B. Expiratory time for triggering (e.g. adjusting E sens up to 50% on the PB840 ventilator)
         C. Triggering sensitivity.
   b If the $FiO_2 \geq 50\%$ or the FiO_2 has increased by $\geq 10\%$ in the previous two hours, consider adjusting PEEP by ≤ 2 cmH_2O up (or down). Consider repositioning the patient and optimising sedation.
   c If secretions are obstructing large airways, or there are significant regions of consolidation, these conditions are unlikely to respond to increases in PEEP and increases in PEEP may impair oxygenation. Thus, if the PEEP is greater than 10 cmH_2O consideration should be given to reducing it.
   d If the above measures do not im prove oxygenation, re-sedate and revert back to the previous controlled ventilation mode (Bi-Level or PC-SIMV+ or equivalent)
   e If the oxygenation has not improved after 12 hours on controlled ventilation, or there is an unanticipated new problem causing deterioration, the partici-

pant should return to their previously assigned ventilation arm (MBV or SPV) e.g.

i. New lung injury / de-recruitment / aspiration/sepsis.

ii. Haemodynamic instability.

iii. Need to return to the operating room or to undergo invasive procedure.

2. If there is continual improvement, proceed towards separation from mechanical ventilation (extubation, or CPAP via a tracheostomy).

6.6 Patient Enrolment and Data Management

6.6.1 Patient Data

Data on patient airway pressure and flow generated from the mechanical ventilator will be recorded using the CURE Software (CURE Soft.) provided with the RCT. The patient data is backed up on regular basis to external storage with encryption applied using VeraCrypt encryption software (VeraCrypt, USA).

Other clinical data also gathered are patient demographics, waveforms, arterial blood gases, routine biochemistry, patient radiology, patient positioning during MV, rescue therapies, loMV and VFD, amount of sedation, duration of ICU stay, frequency and duration of renal support therapies and all causes of ICU, hospital and 90 day mortality.

6.6.2 Blood samples

No person or authority will have access to participant's blood. The blood samples are not stored. They are discarded and incinerated as soon as practicable, in accordance with NZS 4304:2002 'Healthcare Waste Management.

6.6.3 Data Management

All CURE RCT data will be stored at the University of Canterbury (UC). All paper forms (patient sheets, consents, etc) will be scanned and stored at UC. All electronic data will be stored in double encrypted repository and only the participating researchers have access to it. Currently there is no plans on sharing the data but if requested data may be shared. Participants to the study can request their copy of data.

The data will be backed up weekly and again, once participant is finished with the trial and left the hospital. This task will only be performed by the participating researchers. Any protocol variations will be followed-up and noted. The CURE RCT will store data for 20 years.

6.6.4 Study Outcome

The trial will utilise a primary composite end point incorporating area under the curve (AUC) of the P/F ratio over the period of mechanical ventilation. Every participant in the Intervention (MBV) group is compared with every participant in the control (SPV) group. Test statistics will be performed using one-sided Wilcoxon ranksum test at alpha with 0.05. No significance in intervention will also result in the rejection of intervention treatment as a standard of care and thus, the secondary clinical outcome assessments will include the number of desaturation events measured as peripheral capillary oxygen saturation less than 88%, length of mechanical ventilation (LoMV), ventilation free days (VFD) for 28 days, the quality of mechanical ventilation care measured as AUC of SpO_2 /FiO_2 and Chest X-ray Index scores over time. Test statistic will be performed using one-sided Wilcoxon ranksum test at alpha of 0.05.

A difference in primary outcome will show the impact of MBV compared to SPV. No difference would show that enhanced, model-based metrics of patient-specific condition

have no effect on patient-centred or clinical outcomes. Either outcome will yield clinical guidance.

6.6.5 Sample Size Study

A Monte-Carlo simulation was performed to determine the sample size and found a minimum effective sample size of approximately 160 per arm is required to identify a 25% reduction in median LoMV with a 0.8 power at double sided significance level of 5% (Morton et al., 2017).

6.6.6 Stopping Rule

A linear alpha spending approach will be used for early termination of the trial for safety. Linear alpha spending falls between a Pocok and O'Brien-Fleming boundary (Todd et al., 2001). With analysis points of 50, 75, 100, 125 and 160 patients per arm, and an assumed control group mortality of 0.2, the mortality difference required to stop the trial ($\text{Mortality}_{\text{Intervention}} - \text{Mortality}_{\text{control}}$) at each analysis point respectively are: 0.20, 0.16, 0.14, 0.12, 0.10. This approach has cumulative α=0.025.

6.6.7 Safety, Ethics and Dissemination

Ethics Approval has been filed with the New Zealand National Health and Disability Ethics Committee. The CURE RCT clinical protocol and data usage has been filed with the New Zealand South Regional Ethics Committee (Reference number: 14/STH/132). The CURE trial is also registered in the Australian New Zealand Clinical Trial Registry (ACTRN12614001069640).

All results and any subsequent analysis will be published and only the participating investigators will be authors. Currently there is no plan to share data with other organisations. The data collected in this study will also be used for future research.

6.6.8 Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

Adverse events (AEs) are defined as any unexpected change in physiology in a study participant associated with either the maximum recruitment manoeuvre (RM_{Max}) or PEEP adjustment and monitoring procedure (PUMP). This does not necessarily have to have a causal relationship with the above procedures. Typically this would be an unexpected, non-life threatening event, which rapidly resolves following simple corrective measures. For example, hypotension will occur in most participants under-going an RM_{Max}, or PUMP. However if the procedure had to be shortened or abandoned, but the participant recovered with simple corrective measures (e.g. temporarily increasing noradrenaline $\geq$ 5 mcg / min) or giving more than a 500 ml fluid bolus) this would be recorded as an Adverse Event (AE). It is very important these events are accurately recorded as risk factors for AEs need to be defined when carrying out RMs.

Serious adverse events (SAEs) are defined as any untoward medical occurrence that: 1) results in death; or 2) is life-threatening; or 3) prolongs hospitalisation; or 4) results in disability or incapability. However, the baseline mortality of intensive care patients enrolled in the trial will likely be high due to the critical illness necessitating admission to the ICU. Despite attempts at prevention, trial participants will frequently develop life-threatening organ failure(s) unrelated to study interventions. Events that are a part of the natural history of the primary disease process or expected complications of critical illness will not be reported as SAEs in this trial. Additionally, events already defined and reported as study outcomes, such as mortality, re-admission to ICU, will not be labelled and reported separately as SAEs unless they are considered to be causally related to the study intervention or are otherwise of concern in the investigator's judgement.

SAEs will be reported to the principal investigator within 24 hours of any investigator

becoming aware of the event. The minimum information to report includes:

- Patient trial identifier.
- The nature of the event.
- The time the event commenced and ceased.
- An investigator's opinion of the relationship between study involvement and the event (not related, unlikely, possibly, probably or definitely related).
- Whether treatment was required for the event and what treatment was administered.

SAEs could include: pneumothorax; hypotension leading to cardiac arrest; transient desaturation leading to severe or prolonged desaturation; tachycardia, bradycardia, arrhythmia, anaphylaxis and unintended protocol deviations.

In the unlikely event of a physical injury to the participant as a result of their participation in this study, they will be eligible to apply for Accident Compensation Corporation (ACC) NZ within its limitations. If the participant's family/friend have any questions about ACC, they will be able to ask the researchers for more information before they agree to take part in this trial.

ACC cover is not automatic and their case will need to be assessed by ACC according to the provisions of the 2001 Injury Prevention Rehabilitation and Compensation Act. If the claim is accepted by ACC, they still might not get any compensation. This depends on a number of factors such as whether they are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If your relative or friend has ACC cover, generally this will affect their right to sue the investigators.

6.6.9 Data Monitoring Committee

An independent DMC comprising experts in clinical trials, biostatistics and intensive care medicine is established before patient enrolment to review all trial protocols, and oversee and advise this trial. The DMC will be forwarded a copy of all SAE reports as soon as they become available to the trial investigators. The DMC will review all SAE reports that they receive and report back to investigators if any further action is required.

6.6.10 CURE RCT Composition

The steering committee of CURE RCT are the primary investigators Geoff Shaw, Geoff Chase, Chris Pretty and Yeong Shiong Chiew. The clinical data are collected by research nurses in the ICU and mechanical ventilation data and oxygenation (bedside monitor) data will be collected by researchers from UC. All study data will be stored in double encrypted repository at UC. The interpretation of data will be done by participating researchers. The open and close case interim reports will be performed by Paul Docherty and will be performed every 6 months and at 50, and 100 patients. The DMC will have authority on continuation and stopping of the trial based on interim reports.

6.7 Discussion

Mechanical ventilation using PEEP set at minimum elastance has long been investigated in both experimental and clinical trials. These studies ranged from healthy general anaesthesia patients to those with acute respiratory distress syndrome. However, only a few studies have investigated its clinical potential. Recent studies by Pintado et al. (2013) and Chiew et al. (2015c) have shown the potential and feasibility patients ventilated using minimum elastance PEEP. However, setting PEEP based on elastance is problematic due to the increased need of muscle relaxants, protocol burden and potential contradicting findings (Pintado et al., 2013; Chiew et al., 2015c). The pilot trial was also underpowered and thus, a larger clinical trial such as CURE RCT is required to provide

further insight and validate the potential benefit of optimising mechanical ventilation PEEP with model-based methods.

The CURE RCT implements a protocolised staircase PEEP recruitment manoeuvre together with novel computer software to calculate respiratory system elastance in real-time. The computer software, CURE Soft (Szlavecz et al., 2014), uses a single compartment lung model (Brochard et al., 2017) together with other model-based approach (Chiew et al., 2011, 2015a) to aid clinicians during PEEP selection. This process potentially reduces selected PEEP variability and provides more consistent clinical guidance.

There are several limitations of the CURE RCT design that should be noted. In particular, the recruitment manoeuvre is a double staircase and design specific. Studies have reported not all patients benefit from recruitment manoeuvres (Pelosi et al., 2010; Fan et al., 2008), and the benefit of an RM is dependent on the patient-specific disease state, as well as the design of the RM. The double stair-case RM in this trial was designed to assess lung recruitment and provide consistent PEEP titration. It is noted not all patients included in this study will necessarily be recruitable.

Another limitation worth noting is the control group clinical protocol. Clinically, there is relatively little consensus an 'optimal' mechanical ventilation mode. Thus, the standard practice ventilation in the participating hospital relied on general approaches (Brower et al., 2004) and is highly variable between clinicians. There may be no equal comparator for a mechanical ventilation study resulting from this variability. Patients recruited to the CURE RCT will have both intervention and control group MV mode set to Bi-level ventilation. It is debatable that Bi-level may lack certain ventilation advantages. However, this procedure will reduce variability and provides the opportunity for fair comparison between groups.

In the participating ICU, there were more than $>$ 700 patients per year requiring invasive MV. However, only an average of $<$ 5 patients were diagnosed with ARDS as the primary diagnosis per year. ARDS is nearly always regarded as a complication of an acute process. One concern is that the desired sample size cannot be achieved. However, this number is also too low compared to reports (Bersten et al., 2002; Rubenfeld et al., 2005). The low number may be due to the changes of ARDS definition (Villar et al., 2013; Bernard et al., 1994) and misdiagnosis (Estenssoro et al., 2003). Estenssoro et al. (2003) found misdiagnosis could occur due to delayed screening (Estenssoro et al., 2003). Thus, in the CURE RCT, any patient requiring invasive mechanical ventilation is screened immediately, as per Villar et al. (2013), where the P/F ratio is measured at PEEP = 5 cmH_2O, and FiO_2 = 50% (Villar et al., 2013). Equally, a retrospective screening was also performed and found $>$ 200 patients eligible for the trial per year. Hence, a 3-year study is planned for to achieve the target sample size at an estimated recruitment rate of 50%.

6.8 Summary

Optimising patient-specific mechanical ventilator settings remains a huge clinical challenge due to patient disease variability, as well as clinical practice variability. Thus, there is a need of a method to provide consistent patient-specific treatment. The CURE RCT is the first single centre large clinical RCT using model-based minimum elastance PEEP selection in mechanical ventilation. It provides a means to select patient-specific PEEP in a consistent fashion and patient outcomes are compared to current practice. The CURE RCT investigation group hope results from this trial will support the use of model-based methods to estimate optimal PEEP, and will serve as platform to assess other patient-centred outcomes in future mechanical ventilation studies in ARDS /ALI.

The CURE RCT was proposed to start in 2014, it has gone through significant changes and the protocol has only been recently finalised (Kim et al., 2020). This trial will ideally start in 2020 but due to delays in ICU movement at Christchurch Hospital and COVID-19,

it is unknown when trial will officially start.

CHAPTER 7

Neonatal Pulmonary Mechanics in Mechanical Ventilation

7.1 Introduction

Due to pre-maturity and under-development of their lungs, pre-term neonates are susceptible to respiratory distress syndrome (RDS). They thus require mechanical ventilation (MV) to assist breathing (Sweet et al., 2010; Lauterbach et al., 2001; Brown and DiBlasi, 2011). Under-development of the lungs results in reduced alveoli growth and surfactant production (Torday and Nielsen, 1987; Rettwitz-Volk et al., 1998; Polin et al., 2014), resulting in poor gas exchange and non-compliant (stiff) lungs. Invasive MV is utilised to enable gas exchange.

However, Prolonged duration or sub-optimal ventilator settings on preterm infants with invasive MV can result in bronchopulmonary dysplasia (BPD) and ventilator-induced lung injury (VILI), varying from 30-75% among newborns with birth weight less than 1 kg (Kair et al., 2012; Carvalho et al., 2013b; Jobe and Bancalari, 2001). VILI can also result from asynchrony, where the neonate is breathing against the ventilator (Brown and DiBlasi, 2011; Carvalho et al., 2013b; Keszler, 2009; O'Donnell et al., 2004). Thus, MV strategies in this cohort are also focused on reducing MV duration (Brown and DiBlasi, 2011).

MV is common in the neonatal intensive care unit (NICU). While infants exhibit different pulmonary mechanics compared to adults, it still is not widely studied. The use of low tidal volume in adults is a well-accepted approach (Brower et al., 2000) but not in neonates (Chow et al., 2002; Donn and Boon, 2009). In contrast, Brown and DiBlasi (2011) states using tidal volume of 5ml/kg is more beneficial than 3ml/kg in neonates, where both these values are lower than 6-8ml/kg accepted for adults. The gap in these values of 3-5ml/kg is also very large with no consensus on which is better due to primarily to a lack of study (Brown and DiBlasi, 2011). There is thus a need for in-depth understanding of neonatal pulmonary mechanics to better understand and inform MV practice in this cohort.

A study by Bhutani et al. (1988) has used neonatal data and a single compartment model similar to (Bates, 2009; Chiew et al., 2011) to describe neonatal respiratory mechanics. However, this study was limited in both the hardware used (external pneumotachometer and pressure transducer) and the size of the data (20-40 breaths per patient) (Bhutani et al., 1988). It is a near lone study of deterministic modelling of neonatal lung mechanics in the last three decades.

This study is a first in-depth attempt to quantify the underlying lung mechanics for MV

in the NICU (Kim et al., 2019a). It will apply model-based methods, specifically a single compartment model to a clinical data cohort to assess and quantify the underlying elastance and resistance, with a secondary aim to identify the incidence of asynchrony and spontaneous breathing attempts, which can interfere with MV (Chiew et al., 2018; Gutierrez et al., 2011; Thille et al., 2008). If the model translates and successfully captures respiratory mechanics in this cohort, it could be possible to apply a similar model-based MV approach (Morton et al., 2019a; Szlavecz et al., 2014; Chiew et al., 2011) clinically in this cohort. This outcome would offer potential improved, patient-specific care to this cohort in a core area of NICU care significantly impacting outcomes, length of care and stay, and cost.

7.2 Methods

7.2.1 Patient Data and Processing

The NICU ventilation cohort detailed in Section 3.1 is used in this chapter. Airway pressure and flow data from 10 invasively ventilated infants from Christchurch Women's Hospital Neonatal Intensive care unit (NICU) is used. All patients were under standard care and no intervention was performed during data recording. Parental consent was obtained prior to data recording. Ethics for the implementation of this trial and anonymised use of this data was approved by the New Zealand Northern B Health and Disability Ethics Committee (study ref:16/NTB/16).

Waveform data was nominally collected for 24 hours under standard care conditions. Eligibility criteria included the expectation MV would continue for 24 h, clinical equipoise, and general clinically assessed patient medical stability. Informed consent from parents or legal guardians was obtained in all cases.

Patients received either conventional ventilation (CV) or high frequency oscillatory ven-

tilation (HFOV) on a SLE5000 neonatal ventilator (SLE, UK) [30] as determined by standard clinical practice. None of the infants were sedated over the trial period, though some received morphine, which can have a sedative effect (Chase et al., 2004). The clinical characteristics and demographics of patients are shown in Chapter 3 Table 3.1 This table is repeated in this chapter for both clarity and ease of read as Table 7.1.

In cases where an infant was re-intubated after being weaned from MV, or the infant was later switched to another ventilation mode, a subsequent 24 h of data recording was carried out with further parental consent. This second stage allows comparison of lung mechanics over different modes, or changes over time. Infants thus had 1 or more recording periods.

Data was recorded from the ventilator, with no additional re-sampling, smoothing or filtering. Patient data was separated into individual breaths characterised by inspiration (positive flow) and expiration (negative flow). As tiny fluctuations in pressure and flow are observed prior to expiration and/or inspiration onset, additional criteria for inspiration/expiration onset are defined:

- Inspiration start: the first major positive airflow associated with an overall increase in flow (inspiratory flow rate $>$ 16.67 ml/s) and pressure (Pressure increased to P $>$ (PEEP + 2 cmH_20)).
- Expiration start: the first major negative airflow associated with an overall decrease in flow (expiration flow rate $>$ 16.67 ml/s).

Both inspiration and expiration start is checked over 20 data points to ensure there is a consistent increase/decrease in flow and PEEP. Expiration is defined as a major negative airflow decaying towards zero followed by inspiratory postive flow at the next breath.

As pressure-flow profiles can be interrupted, or modified by clinical care or patient asynchrony, additional criteria were applied to identify 'true' breaths from the raw signal data:

- Total inspiratory volume was $>$ 0.5 ml
- PIP was $>$ (PEEP + 1 cmH_20)
- Expiration was identified within 1.1 s of the calculated onset of inspiration defined above, where standard CV respiratory rates(RR) are 60/min or 1 s for both inspiration and expiration.

These criteria eliminate asynchronous and small partial breaths.

Table 7.1: Clinical characteristics of recruited NICU patients, repeated from Chapter 3 Table 3.1

Patient	Ventilation Mode	Gender	Gestational Age at birth (weeks)	Post-natal age (days)	Weight(g)		Days of MV	Steroids			Surfactant therapy	Morphine		Clinical Notes
					Birth	Trial		Prenatal	Postnatal	During recording		Y/N	Dose [mcg/kg/h]	
1	HFOV	F	26.5	31	760	1120	22	Y	N	Y	N	Y	12	RDS, severe lung disease
2	HFOV	F	25	21	570		21	Y	Y	N	N	Y	?	Severe lung disease, previous sepsis/pneumonia
	CV - PTV + TTV			23		770	23			Y			PO	Severe RDS, CNS Sepsis, PPHN
	CV - PTV + TTV			32		890	27		N	N			PO/5**	
3	CV - SIMV + TTV	M	41.5	3	3400	3400	3	N	Y	?	N	Y	10	Severe Hypoxic Ischemic Encephalopathy, seizures
4	CV - PTV + TTV	F	37	2	2750	2750	2	N	N	-	N	Y	6	PPHN
5	HFOV	F	29.9	0	1580	1580	1	Y	N	-	Y	N	-	MCDA twin, Maternal Preeclampsia Toxaemia
	CV - PTV + TTV			2										
6	CV - PTV + TTV	M	27.4	2	1170	1170	1	Y*	N	-	N	Y	?	Oesophageal atresia, post op from surgery
7	CV - PTV + TTV	F	28.1	45	960	1990	5	Y	N	-	Y	Y	20	Abdominal surgery
8	CV - PTV + TTV	F	25.7	2	770	770	2	N	N	-	Y	N	-	RDS
9	CV - PTV + TTV	M	25.3	4	820	-	5	Y*	N	-	N	Y	?	RDS
10	CV - PTV + TTV	M	25.9	4	810	810	1	Y*	N	-	N	N	-	RDS

* Partial course only. ** oral changed to infusion at stated rate.

HFOV: High frequency oscillatory ventilation. CV: Conventional ventilation. PTV: patient triggered ventilation.

PSV: pressure support ventilation. TTV: Targeted tidal volume.

RDS: Respiratory Distress Syndrome. PPHN: Persistent pulmonary hypertension of the newborn.

CNS: central nervous system. MCDA twins: monochorionic diamniotic twin gestation.

7.2.2 Model and Identification

The single compartment model described in Section 2.2, Eq (2.3) is used to identify NICU pulmonary mechanics. However, the pressure loss across the endotracheal tube (ETT) may be significant in NICU, as their small ETT diameters (3-5mm) can significantly increase resistance to flow and must be considered. Thus, Jarreau's equation described in Chapter 2 Section 2.5, Eq (2.9) is incorporated into the single compartment model. The single compartment model using this term to account for ETT pressure loss is presented in Chapter 2, Eq (2.10) and is repeated in this chapter for clarity and ease, where the model is defined:

$$P_{aw} = E_{rs}V + R_{rs}Q + PEEP + \Delta P_{ETT} \tag{7.1}$$

Where, P_{aw} is the airway pressure, E_{rs} is the elastance, V is the volume, R_{rs} is the airway resistance, Q is the flow, $PEEP$ is the pressure offset, and ΔP_{ETT} is the pressure loss across the ETT, specifically defined in Eq (2.9).

The ETT diameter is a function of patient weight. The typical size of ETT diameter are 3-5 mm. ETTs are clinically shortened patient-specifically by 1-2 cm post-insertion. The shortened length was unavailable for this NICU cohort and therefore was assumed all ETTs are shortened by 2 cm providing a minimum estimation of ΔP_{ETT}, where R_{rs} may capture additional resistance due to longer lengths. Table 3.2 from Chapter 3 is repeated in this chapter for ease of read as Table 7.2

Table 7.2: Clinical guidelines for ETT selection repeated from Chapter 2 Table 3.2

ETT diameter [mm]	Un-shortened ETT length [cm]	Indication for use
2.0	-	Cannot insert a 2.5 mm ETT
2.5	18	Weight $<$ 1.5 kg
3.0	19.5	Weight 1.5 - 2.5 kg
3.5	20	Weight 2.5 - 4.0 kg
4.0	-	Weight $>$ 4 kg

7.2.3 Analysis

This study only examines model fit to conventional ventilation data. Data from Patient 1 was excluded because they were recorded in only HFOV mode, where preliminary analysis suggests pressure characteristics are more a function of the ventilator, rather than patient specific lung mechanics, due to the rapid Respiratory Rate (RR = 300+/min). An analysis of HFOV was thus deemed out of scope in this study, leaving N = 9 patients (Patients 2–10 in Table 7.1).

Elastance (E_{rs}) is fit breath-to-breath, and resistance (R_{rs}) is fit using a moving window of 30 breaths to avoid mild parameter trade-off between E_{rs} and R_{rs}. in identifying Eq (7.1) (Docherty et al., 2011; Chiew et al., 2011). This moving window reduces variability, and improves both identifiability and breath-to-breath consistency in identified values.

In particular, the model used in this study is focused on non-spontaneous breathing (Chiew et al., 2011). Non-sedated infants cry, try to breath spontaneously, and have clinical interactions, causing asynchronous breaths, all of which can be detected by the model (Kannangara et al., 2016a, 2018; Redmond et al., 2019; Major et al., 2016b; Damanhuri et al., 2016, 2019; Chiew et al., 2011, 2018; Newberry et al., 2016; Kannangara et al., 2016b). These asynchronous breaths do not yield the patient's true underlying pulmonary mechanics or condition as these events distort the pressure and flow waveforms, and spontaneous breathing provides a negative pressure, which trades off with the positive pressure supplied by ventilator.

This study aims to capture these underlying lung mechanics in neonates and thus, some breaths are eliminated for this analysis. Further filtering criteria used to remove outlier breaths and/or poor model fits include:

- Model-fit error $> 15\%$
- Model-based $E_{rs} \leq 0$ (un-physiological, occurs with spontaneous effort (Chiew et al., 2015a))
- Model-based E_{rs} outside 5^{th} and 95^{th} percentiles as the focus is on central behaviour and mechanics.

Model fit is assessed using the percent mean absolute relative difference (MARD). Data is presented as median and [IQR] (interquartile range), unless specified otherwise.

Model fitting error $> 15\%$ are discarded for this analysis because fitting error $> 15\%$ indicates that model does not accurately represent patient's physiological condition (Chiew et al., 2011). Considering this analysis is a proof of concept study attempting to quantify NICU pulmonary mechanics, including breaths with error $> 15\%$ is not included.

Different subgroup comparisons were carried out to validate the identified model-based elastance against clinically and physiologically expected trends. Elastance and resistance are compared in infants who received surfactant treatment to untreated infants, where surfactant is expected to reduce elastance. However, it is difficult to directly compare patients treated with surfactant and not treated with surfactant due to the large range of weight, as larger infants would have more developed lungs (Brown and DiBlasi, 2011). Thus, specific compliance is used to normalise to weight and adjust for this factor.

Specific compliance is often used metric in neonatal MV as it is a measure of intrinsic elasticity of the lung tissue while being independent of lung volume (Phelan and Williams, 1969). Compliance is an inverse of elastance, and specific compliance can be calculated by dividing compliance by the weight (Kannangara et al., 2018). Thus, specific

elastance can be calculated using:

$$C_{specific} = \frac{C}{m} = \frac{1}{E_{rs}} \times \frac{1}{m} = \frac{1}{E_{rs} \times m} \tag{7.2}$$

Therefore $E_{specific}$ is defined:

$$E_{specific} = E_{rs} * m \tag{7.3}$$

Where, C is the compliance and m is the mass of the infant.

Because infant size is a factor affecting respiratory mechanics, increased birth weight is expected to result in decreased elastance due to more developed lung structures and larger volumes (Kannangara et al., 2018). Therefore, different birth weight groups are compared based on the hypothesis larger infants would have lower elastance. As they are compared by weight, elastance, E_{rs}, is used directly.

7.2.4 Statistics

All statistical comparisons are made using non-parametric statistics due to non-Gaussian distributions. Statistically as noted, to get the main or broad central tendency of behaviour the 90% range of results for each infant is analysed. Due to very large data sets and smaller number of patients, bootstrapping was used to examine the difference in median values, in each comparison (Motulsky, 1995). Data was bootstrapped 10,000 times with replacement. A 99% Confidence Interval (CI) for difference in median specific elastance values are created. If the CI does not cross zero, differences in medians are statistically significant with $p \leq 0.01$, which is more conservative than $p \leq 0.05$ because of multiple comparisons and very large data vectors (Motulsky, 2015).

This bootstrapping statistical comparison is chosen between surfactant and non-surfactant cohort. Patients are not individually compared, but compared as whole group instead. 10,000 data are randomly chosen from each surfactant and non-surfactant cohorts with

replacement. Then the difference in medians and mean of medians are calculated. This is repeated another 10,000 times and 99% CI is calculated.

7.3 Results

7.3.1 Breaths and Asynchrony

Airway pressure and flow data were recorded for 10 patients, comprising 205.9 hours of conventional ventilation (CV; N= 9; Patients 2-9), and 53 hours of HFOV (N = 3; Patients 1,2,5). Measured ventilator outcomes are given in Table 7.3 for the conventionally ventilated patients analysed here. Patient 2 had three different recording sessions (2 CV, 1 HFOV). However, due to technical difficulties resulting in a loss of laptop power, the CV recordings were cut to 2 and 3 hours. Patient 5 has $<$24 hours of data in CV as they started with HFOV, but switched to CV. In many cases, total hours per patient was slightly $<$24 hours due to these issues, extubation, or other clinical factors. Patient 2 episode 2 (2-2 in Table 7.3) had the minimum number of breaths with 4110, and Patient 10 had the maximum of 93185. Table 7.3 also shows number of filtered breaths per patient. From this table it can be seen the PSV and SIMV mode creates a higher occurrence of fitting error and extremities in elastance, as they have more filtered breaths in comparison to those on PTV.

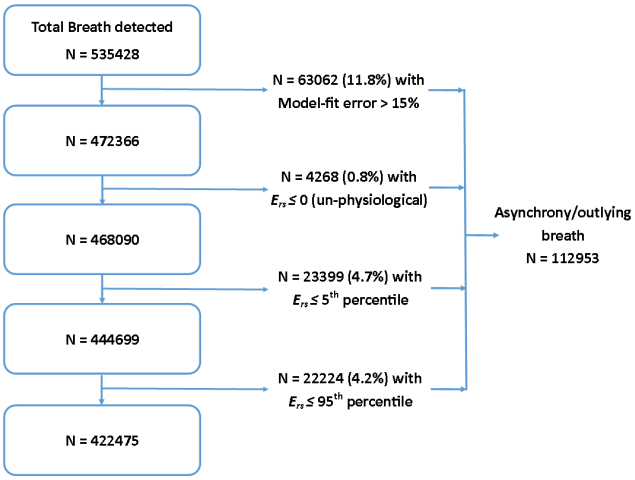

Figure 7.1: Consort diagram showing tabulated post filtering process. Percentages reflect percentage of total breaths detected.

Figure 7.1 shows filtering criteria used to remove further outlier breaths and/or poor model fits with total number still left. Most breaths removed using this filtering criteria were unusual breaths with significant spontaneous breathing effort, or effects in the pressure-flow profiles caused by clinical interactions with the infant. Examples of filtered breaths due to significant spontaneous breathing and/or clinical interaction are shown in Figure 7.2, where it is clear these breaths were not representative of the underlying lung mechanics in the infants typical breathing pattern, and were thus excluded. Between initial filtering and post-fitting filtering, a total of 112,953 of 535,428 (21%) breaths were excluded as asynchronous or otherwise altered, leaving 422,475 breaths over the n=9 infants.

Table 7.3: Clinical characteristics of recruited NICU patients

			Ventilator settings							Recorded outcomes				
Patient	Ventilation mode	Day of MV	PEEP (cmH2O)	Target Tidal Volume ml/kg	Target Tidal Volume ml	Surfactant therapy	Hours of Recording	Number of Breaths*	Filtered Breaths	Median [IQR] delivered inspired tidal Volume [ml]	Max PIP [cmH2O]	Median [IQR] PIP [cmH2O]	Median [IQR] PEEP [cmH2O]	Median [IQR] Ti[s]
2-2	CV - PTV +TTV	23	5	5	4	N	2	4110	676	4.4 [3.8 - 5.6]	18.3	10.5 [9.5 - 13.2]	5.1 [5.0 - 5.1]	0.4 [0.4 - 0.5]
2-3	CV - PSV + TTV	27	5	5	4	N	3	8695	2325	5.1 [4.3 - 5.9]	22.9	10.0 [9.2 - 12.5]	5.5 [5.5 - 5.6]	0.4 [0.4 - 0.5]
3	CV - SIMV + TTV	3	5	3.8	13	Y	21	60322	36642	21.6 [18.2 - 25.0]	21.1	9.7 [9.4 - 10.4]	5.1 [5.0 - 5.2]	0.4 [0.4 - 0.5]
4	CV - PTV + TTV	2	5	4	11	Y	19.3	52590	10063	12.1 [10.7 - 14.1]	19.1	9.7 [8.5 - 12.6]	4.3 [4.2 - 4.5]	0.4 [0.4 - 0.5]
5	CV - PTV + TTV	1	5	5	7.9	N	8.2	25346	4606	8.6 [7.7 - 9.5]	32.8	9.5 [9.3 - 9.6]	5.1 [5.1 - 5.2]	0.4 [0.4 - 0.4]
6	CV - PTV + TTV	1	5	4.3	5	Y	21	74081	8327	5.0 [4.8 - 5.3]	25.6	16.5 [15.2 - 18.6]	5.5 [5.4 - 5.5]	0.4 [0.4 - 0.4]
7	CV - PTV + TTV	5	5	4	6.6	N	23.6	60109	9364	6.2 [5.7 - 6.9]	26.9	13.0 [11.2 - 14.6]	6.0 [6.0 - 6.1]	0.4 [0.4 - 0.4]
8	CV - PTV + TTV	2	5	3.9	3	N	22	72905	12210	3.2 [2.9 - 3.6]	21.8	10.3 [9.2 - 12.2]	4.8 [4.7 - 5.0]	0.4 [0.3 - 0.4]
9	CV - PTV + TTV	5	5	4.2	4	Y	24.6	84085	14495	4.8 [4.3 - 5.2]	27.8	17.8 [14.8 - 19.9]	4.7 [4.7 - 4.8]	0.3 [0.3 - 0.4]
10	CV - PTV + TTV	1	5	5	4	N	42.8	93185	14245	3.7 [3.4 - 4.0]	22.8	12.3 [11.1 - 13.8]	4.7 [4.6 - 4.7]	0.4 [0.3 - 0.4]

* Filtered out breaths with poor fitting error and extremes in elastance. HFOV: High frequency oscillatory ventilation. CV: Conventional ventilation. PTV: Patient triggered ventilation.

PSV: Pressure supported ventilation. TTV: Targeted tidal volume. Ti = inspiration time

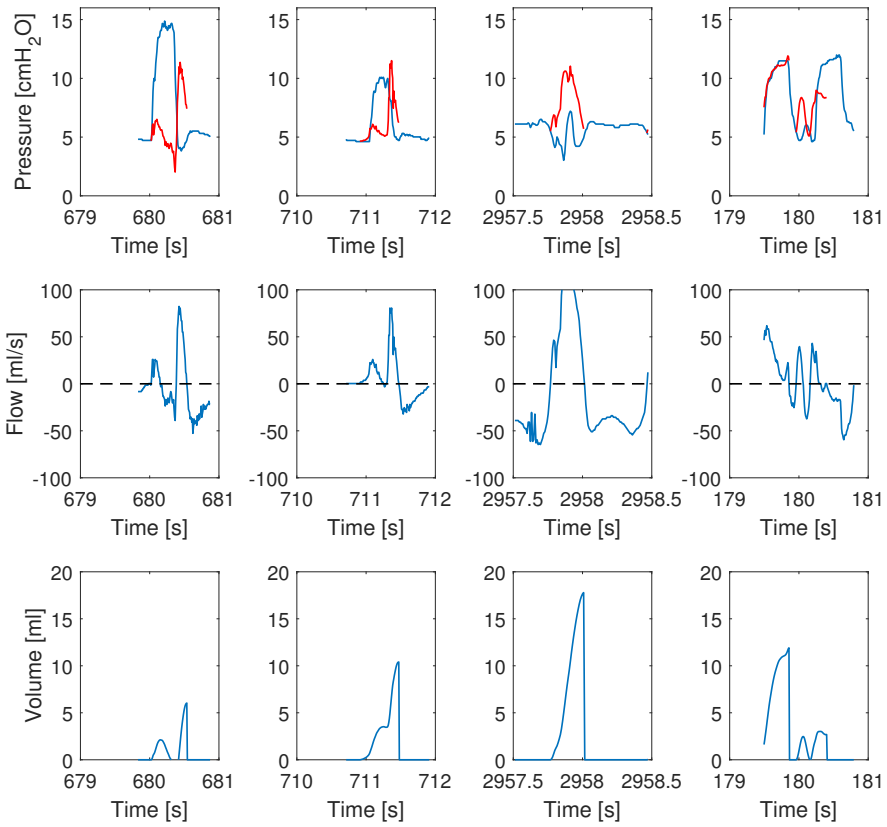

Figure 7.2: Four examples of excluded breaths showing poor model fit (red) along with the corresponding pressure-flow and volume profiles (blue).

Table 7.4 shows mean and standard deviation of PEEP, driving pressure (ΔP), and volume/target volume per patient of normal and filtered breath. It can be seen that the standard deviation for filtered breaths are higher. Filtered breaths have higher standard deviation, as they are mostly asynchronous and/or spontaneous breathing.

Table 7.4: Mean and standard deviation of PEEP, driving pressure (ΔP) and volume/target volume for normal and filtered breaths.

	PEEP				ΔP				V/targetV			
	Normal breath		filtered breath		Normal breath		filtered breath		Normal breath		filtered breath	
Patient	mean	std	mean	std	mean	std	mean	std	mean	std	mean	std
2*	5.38	0.28	5.59	0.57	11.44	2.96	11.55	3.44	0.98	0.23	0.95	0.39
3	5.59	0.17	5.63	0.46	10.23	1.66	7.84	2.39	5.43	1.62	6.68	6.53
4	4.62	0.13	4.7	0.41	10.98	3.03	10.78	3.55	3.12	0.74	4.03	2.49
5	5.36	0.19	5.31	0.7	9.78	0.93	9.93	2.65	1.71	0.29	1.73	0.87
6	5.61	0.32	5.68	0.88	16.85	2.58	16.7	3.61	1.17	0.15	1.23	0.47
7	6.18	0.22	6.23	0.45	13.45	2.71	13.94	3.76	1.6	0.32	1.95	0.87
8	5.14	0.76	5.24	0.84	11.33	2.63	11.2	2.65	0.86	0.23	0.96	0.5
9	4.97	0.45	5.04	0.79	17.34	3.69	15.52	5.22	1.14	0.26	1.35	0.71
10	4.8	0.17	4.85	0.45	11.85	1.87	11.85	2.6	0.76	0.12	0.84	0.32
ALL	5.24	0.61	5.37	0.74	13.36	3.81	11.3	4.45	1.55	1.26	3.26	4.57

* Patient 2-2 and 2-3 are merged under 2 due to smaller number of breaths

7.3.2 Cohort Elastance and Resistance

The single compartment model with ETT compensation in Eq (7.1) was fit to every breath. Overall, model fit was very good with median [IQR] percentage MARD of 5.7 [5.2-6.3]% across all conventionally ventilated patients. Elastance across all patients was median 1.622 [0.854 - 2.253] cmH_2O/ml and resistance was median of 5.223 [0.000 - 33.851] $cmH_2O.s/ml$. The median [IQR] of elastance, resistance and MARD across 6 hourly time intervals (21600 breaths per patient) are given in Table 7.5. Figure 7.3 shows a range of fitting outcomes, demonstrating extremely good fit (MARD, 2.27%), good fit with spontaneous breathing effort causing a dip in pressure at inspiration onset (MARD, 6.93%), and relatively poor fit (MARD, 11.50%).

Table 7.5: Mechanical Ventilation characteristics of recruited patients on conventional ventilation (CV). Elastance (E_{rs}) is in cmH_2O/ml, and Resistance (R_{rs}) is in cmH_2O.s/mL.

		Median [IQR]				
Patient		Hours: 1-6	Hours: 7-12	Hours: 13-18	Hours: 19-24	Overall
2-2	E_{rs}	1.24 [0.76 - 2.08]				1.20 [0.76 – 2.08]
	R_{rs}	0.00 [0.00 - 0.00]				0.00 [0.00 – 0.00]
	%Mard	5.39 [4.13 - 7.80]				5.39 [4.13 – 7.80]
2-3	E_{rs}	0.78 [0.57 - 1.62]				0.78 [0.57 – 1.62]
	R_{rs}	0.00 [0.00 - 0.00]				0.00 [0.00 – 0.00]
	%Mard	8.58 [7.09 - 0.29]				8.58 [7.09 – 0.29]
3	E_{rs}	0.16 [0.11 - 0.23]	0.14 [0.09 - 0.20]	0.14 [0.10 - 0.19]		0.14 [0.10 - 0.21]
	R_{rs}	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.00]		0.00 [0.00 - 0.00]
	%Mard	8.05 [6.78 - 9.87]	8.33 [6.78 - 0.28]	8.23 [6.38 - 10.84]		8.20 [6.66 - 10.32]
4	E_{rs}	0.49 [0.29 - 0.74]	0.46 [0.24 - 0.75]	0.27 [0.18 - 0.47]		0.39 [0.23 - 0.67]
	R_{rs}	0.02 [0.01 - 0.03]	0.03 [0.02 - 0.04]	0.01 [0.00 - 0.02]		0.02 [0.01 - 0.03]
	%Mard	6.27 [5.20 - 8.09]	6.33 [5.26 - 7.99]	6.65 [5.52 - 8.26]		6.43 [5.32 - 8.11]
5	E_{rs}		1.67 [1.31 – 1.92]			1.67 [1.31 – 1.92]
	R_{rs}		0.00 [0.00 – 0.00]			0.00 [0.00 – 0.00]
	%Mard		6.05 [4.80 – 7.73]			6.05 [4.80 – 7.73]
6	E_{rs}	2.79 [2.55 - 2.98]	2.12 [1.90 - 2.29]	1.87 [1.69 - 2.06]		2.18 [1.87 - 2.60]
	R_{rs}	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.01]	0.00 [0.00 - 0.00]		0.00 [0.00 - 0.00]
	%Mard	3.83 [3.22 - 4.58]	3.12 [2.65 - 3.88]	2.91 [2.33 - 3.83]		3.31 [2.68 - 4.22]
7	E_{rs}	1.21 [0.92 - 1.49]	1.12 [0.91 - 1.30]	0.90 [0.65 - 1.21]	0.65 [0.49 - 0.92]	1.01 [0.68 - 1.28]
	R_{rs}	0.08 [0.06 - 0.12]	0.05 [0.04 - 0.06]	0.06 [0.04 - 0.08]	0.05 [0.04 - 0.07]	0.06 [0.04 - 0.08]
	%Mard	6.29 [4.98 - 8.20]	5.03 [4.21 - 6.33]	5.64 [4.67 - 7.32]	5.54 [4.54 - 7.18]	5.58 [4.55 - 7.28]
8	E_{rs}	1.39 [1.11 - 1.78]	1.46 [1.16 - 1.84]	2.13 [1.49 - 3.21]		1.58 [1.23 - 2.16]
	R_{rs}	0.03 [0.01 - 0.06]	0.00 [0.00 - 0.01]	0.04 [0.01 - 0.07]		0.02 [0.00 - 0.05]
	%Mard	5.82 [4.11 - 8.26]	4.45 [3.39 - 6.11]	5.42 [3.99 - 7.33]		5.13 [3.73 - 7.23]
9	E_{rs}	2.99 [2.73 - 3.21]	2.73 [2.03 - 3.23]	2.70 [2.02 - 3.09]	2.36 [1.70 - 2.78]	2.73 [2.11 - 3.11]
	R_{rs}	0.03 [0.02 - 0.04]	0.04 [0.02 - 0.07]	0.03 [0.02 - 0.04]	0.01 [0.00 - 0.02]	0.03 [0.01 - 0.04]
	%Mard	4.59 [3.88 - 5.68]	6.46 [4.69 - 8.85]	5.72 [4.32 - 8.01]	6.51 [5.14 - 8.34]	5.70 [4.34 - 7.81]
10	E_{rs}	1.64 [1.26 - 2.20]	1.67 [1.31 - 1.92]	1.73 [1.45 - 1.95]	1.88 [1.59 - 2.11]	1.74 [1.38 - 2.02]
	R_{rs}	0.00 [0.00 - 0.02]	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.00]	0.00 [0.00 - 0.01]	0.00 [0.00 - 0.00]
	%Mard	6.66 [5.51 - 8.19]	6.02 [4.79 - 7.67]	5.49 [4.43 - 7.19]	5.48 [4.44 - 7.36]	5.95 [4.71 - 7.66]

* Patients 2-2 and 2-3 did not have enough recording time for 6 hourly time frame therefore median IQR represents 3 hours.

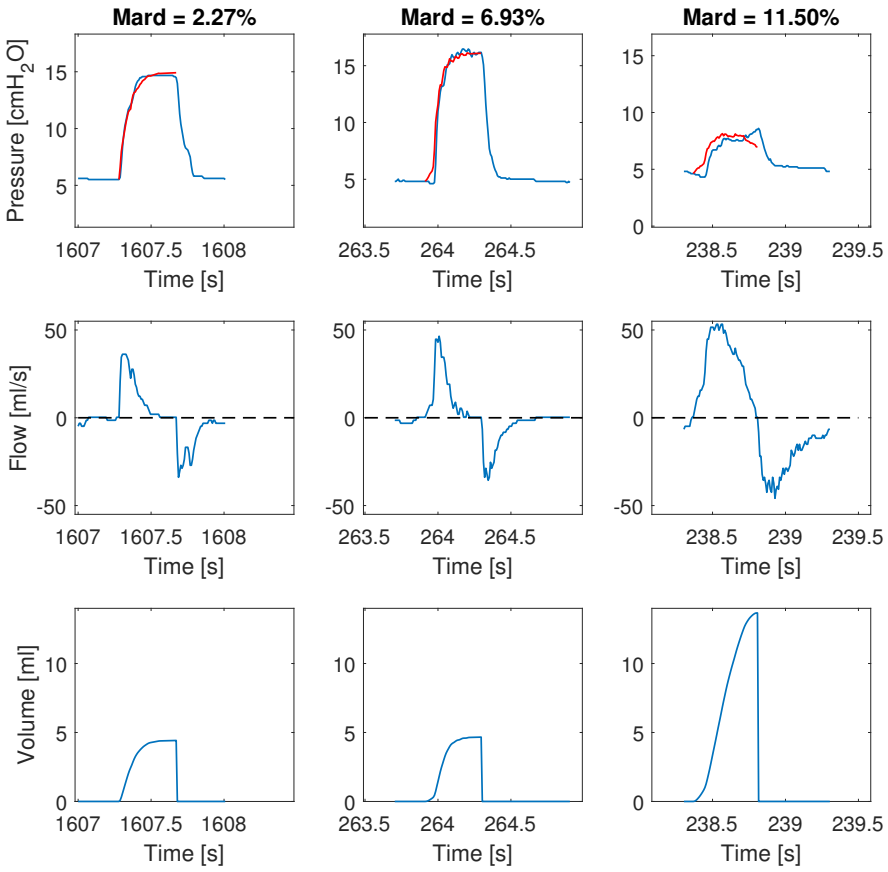

Figure 7.3: Three examples of model fit (red) showing low MARD (2.27%), medium MARD (6.93%) and high MARD (11.5%)

7.3.3 Subgroup analyses: Surfactant

Patients treated with surfactant, shown in Table 7.6, had significantly lower specific elastance than those without the treatment, as seen in Figure 7.4 showing the expected response to treatment (Baraldi and Filippone, 2007; Yuksel et al., 1993; Wood and Jobe, 1993). The difference of the median of specific elastance with 99% CI is -0.48 [-0.49 -0.48] $cmH_2O.kg/ml$, showing a $p \leq 0.01$ statistically significant difference in specific elastance. Resistance is similar across both cohorts as the difference of the median of resistance with 99% CI is 0.21 [-0.12 0.53] $cmH_2O.s/ml$.

As surfactant lowers surface tension, lowering the pressure required to keep alveoli and airways open. Thus, a reduction or lower value of respiratory elastance in patients treated with surfactant is expected. This result thus shows the model's ability to capture

a known response to typical care Baraldi and Filippone (2007); Yuksel et al. (1993); Wood and Jobe (1993); Brown and DiBlasi (2011); Carvalho et al. (2013b).

Table 7.6: Patient characteristics of selected patients who were and were not treated with surfactant

	Subject	Study Weight [g]	Day of MV	Morphine	Target V_t[ml]	ETT diameter [mm]
Treated with Surfactant	5	1580	1	Y	7.9	3.0
	8	770	2	N	3	2.5
Not Treated with Surfactant	2	890	27	Y	4	2.5
	3	3400	3	Y	13	2.5
	4	2750	2	Y	11	3.5
	6	1170	1	Y	5	3.5
	7	1990	5	Y	6.6	3.0
	9	820	5	Y	4	2.5
	10	810	1	N	4	2.5

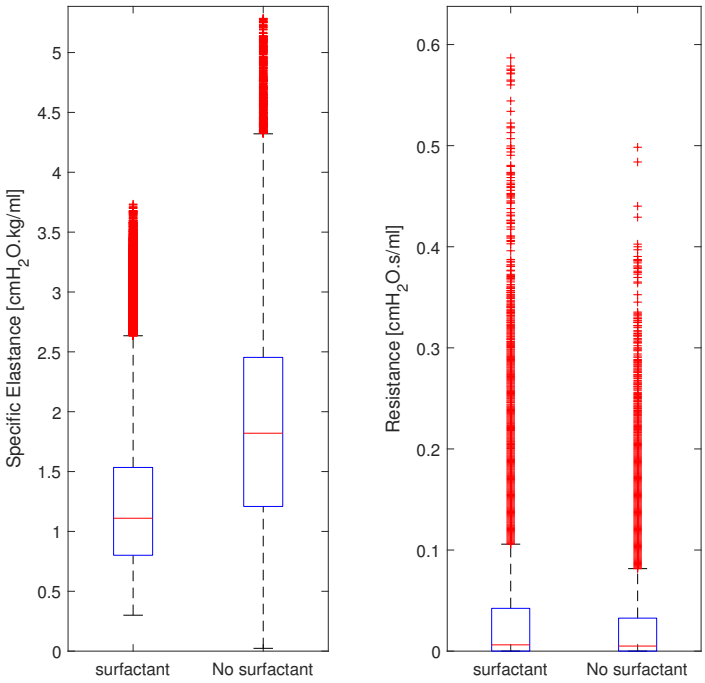

Figure 7.4: Specific elastance and resistance in subgroups of patients (5, 8; N = 81,435 breaths) with surfactant therapy, and patients (2, 3, 4, 6, 7, 9, 10; N = 341,040 breaths) without surfactant therapy.

7.3.4 Subgroup analyses: Weight based trends

Elastance decreased with increasing weight, as seen in Figure 7.5 and Table 7.7 ($p \leq 0.01$ in all comparisons). This result is expected, as PEEP and the plateau pressure remain largely the same over all these the patients, and thus effective elastance drops due to

increasing in tidal volume. This result may also reflect greater lung maturity with increasing infant weight (and maturity) resulting in lower, less stiff lungs (Hislop et al., 1986). Resistance was similar, as expected.

Table 7.7: Patient characteristics of selected patients who were and were not treated with surfactant

	Subject	Study Weight [g]	Day of MV	Surfactant	Morphine	Target V_t [ml]	ETT diameter [mm]
<1000g	2	890	27	N	Y	4	2.5
	8	770	2	Y	N	3	2.5
	9	820	5	N	Y	4	2.5
	10	810	1	N	N	4	2.5
1000g-2000g	5	1580	1	Y	Y	7.9	3.0
	6	1170	1	N	Y	5	3.5
	7	1990	5	N	Y	6.6	3.0
>2000g	3	3400	3	N	Y	13	2.5
	4	2750	2	N	Y	11	3.5

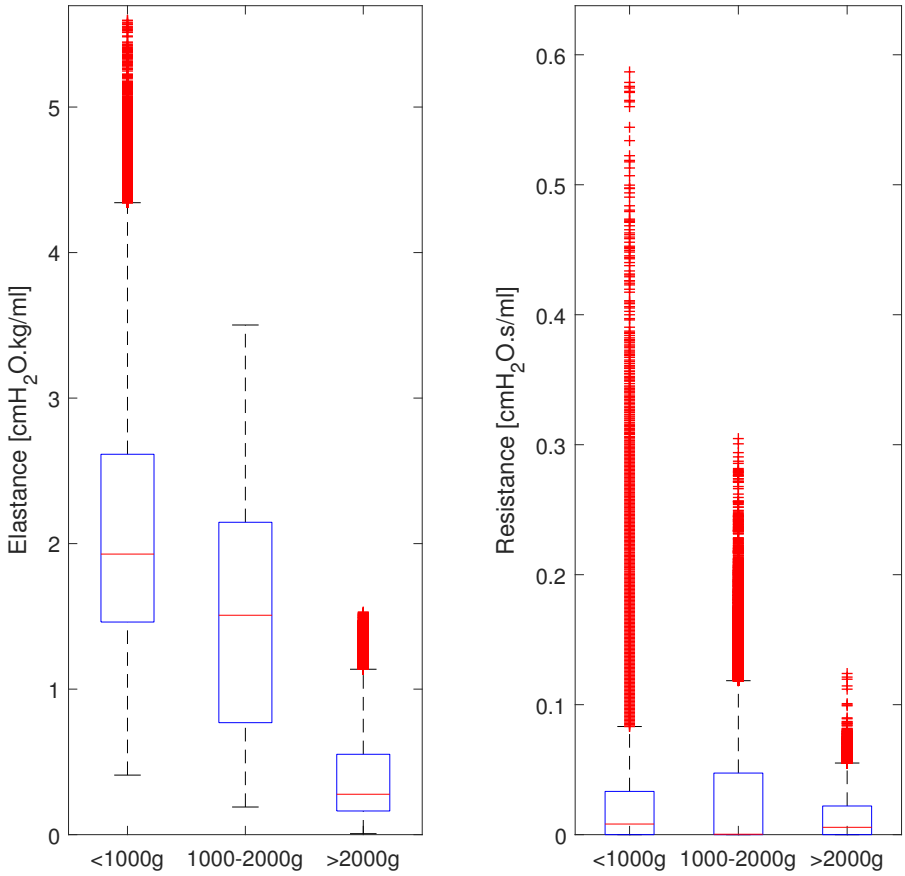

Figure 7.5: Model-based elastance and resistance in selected patients grouped by weight with <1000g (Patients 2, 8, 9, 10; N = 219,029 breaths); 1000-2000g (Patients 5, 6, 7; N = 137,239 breaths); >2000g (Patients 3, 4; N = 66,207 breaths).

7.4 Discussion

7.4.1 Breaths and Asynchrony

A total of 422,475 (79%) of identified breaths from raw data were used in the model-based analyses, and 112,953 (21%) breaths were removed. The breaths filtered out primarily represent significant spontaneous breathing and/or clinical interactions affecting the pressure-flow waveforms. These breaths are thus asynchronous for one or more of these reasons, and per Figure 7.2, and do not represent typical MV supported breaths determined primarily or solely by the underlying fundamental pulmonary mechanics. The authors could find no prior studies of this scale to compare this incidence rate, which is clinically large and potentially unexpected.

Table 7.4 shows mean and standard deviation of PEEP, driving pressure and volume/-targeted volume for normal and filtered breaths. The filtered breaths shown to have higher standard deviation, these breaths are much more variable. High variability in standard deviation implies either asynchrony or spontaneous breathing effort.

Many of the breaths that were filtered are 'odd' breaths like those shown in Figure 7.2, and the standard deviation is higher in filtered breaths in comparison to normal breaths shown in Table 7.4. For these reasons, the 21% filtered breaths are considered asynchronous or highly spontaneous breathing efforts. It should also be noted that Chiew et al. (2011), states that fitting error $>$15% does not represent patient physiological condition (Chiew et al., 2011).

Table 7.5 shows number of filtered breaths. It can be seen PSV and SIMV modes have higher number of breaths removed. Patient 3 who was ventilated using SIMV mode has significantly high number of breaths removed compared to other patient and ven-

tilation modes. However, Patient 3 was most developed infant with weight of 3400g, gestation age of 41.5 weeks and severe hypoxic ischemic encephalopathy and seizures. However, given the lack of patient numbers and data on other SIMV ventilation modes, it is hard to determine whether the ventilation mode itself is the cause for such large number of breaths removed. Patient 2 was on both PTV and PSV modes. When comparing PTV to PSV modes for this patient, PSV mode can be considered to give results with a higher incidence of filtered breaths.

7.4.2 Cohort Elastance and Resistance

A single compartment lung model is used with clinical data to capture respiratory mechanics in the NICU patients. Model fit error (MARD) was 5.7 [5.2 – 6.3]%. Overall results were consistent across weight and a known therapy directly affecting elastance for a smaller number of infants in these subgroups. Thus, based on this first analysis, the model can be used without further alteration to Eq (7.1) to estimate clinical breath-to-breath lung mechanics, specifically, elastance and resistance, in this cohort.

Elastance and resistance values across all conventionally ventilated patients are given in Table 7.5. Elastance differed significantly within and between patients. Elastance also differed significantly across periods as short as 30 seconds (30 breaths) due to commonly occurring increases in PIP, as shown in Figure 7.6 and Figure 7.7. Elastance can be approximated by change in pressure over change in volume. Thus, a doubling in PIP, with no change in tidal volume, will result in a doubling of elastance for that breath. This outcome is clearly seen in Figure 7.8, where elastance changes with increases in PIP, while inspired tidal volume remains roughly the same. These increases in elastance may reflect periods of patient relaxation/weakness with no spontaneous breathing, or clinical interactions compressing the thorax, muscle tension, or crying. Unfortunately, all these potential observations were not directly recorded at the bedside, and thus remain to be confirmed.

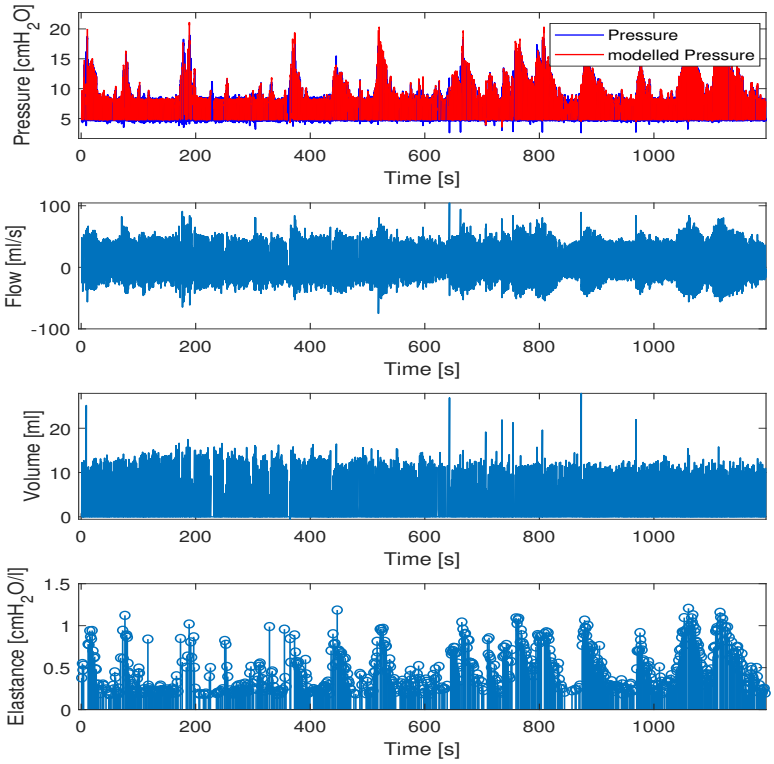

Figure 7.6: Raw data from 20minutes of ventilation in Patient 4 showing significant and periodic increases in PIP.

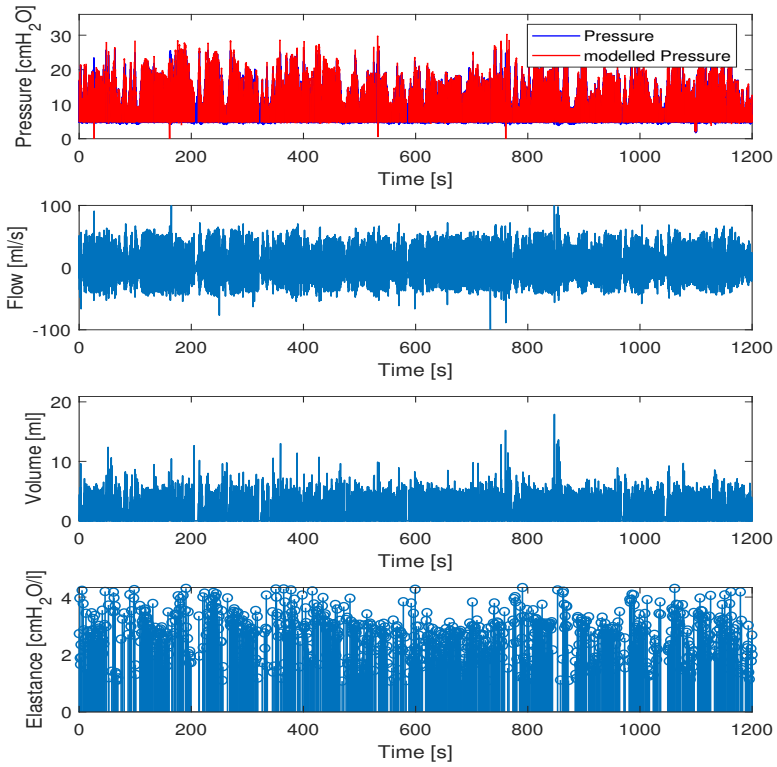

Figure 7.7: Raw data from 20minutes of ventilation in Patient 9 showing significant and periodic increases in PIP.

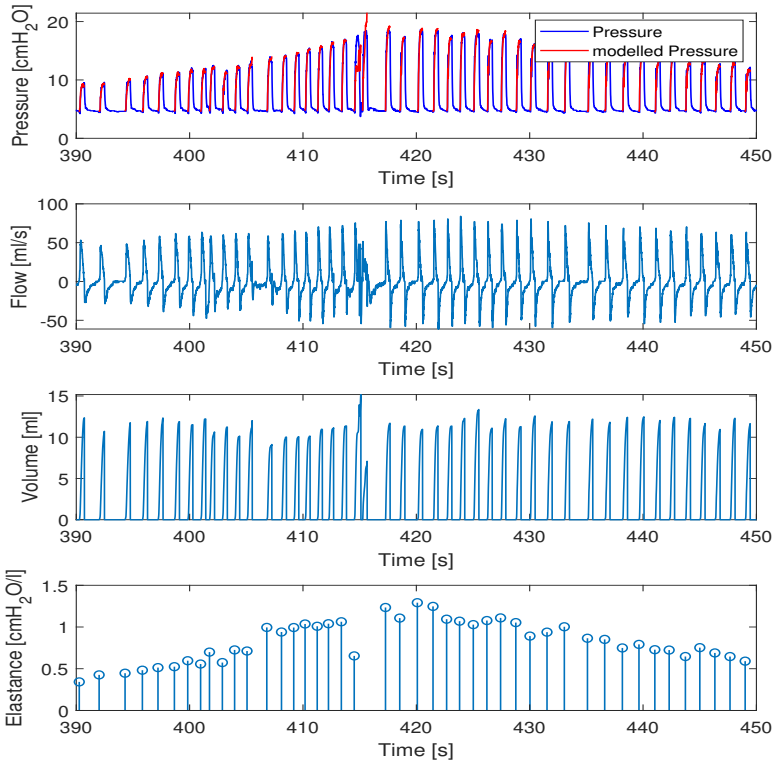

Figure 7.8: PIP increase and decrease over period of 60 seconds for Patient 4 in hour 8 of recording

Underlying intra-patient variability is large. As shown in Table 7.5, both intra- and inter-patient elastance (E_{rs}) differs largely over a 24 hour period. Large inter-patient variability is expected, as patients have different birth weights, degrees of prematurity, and clinical diagnoses and co-morbidities. However, the observed intra-patient elastance (E_{rs}) is unexpectedly variable in comparison to adult MV (Kim et al., 2017).

Some patients were observed (Table 7.5) to have zero model-fit resistance (R_{rs} = 0) because the ΔP_{ETT} term captures the main contribution to resistance without any additional requirement for an additional resistance term This result matches these seen in adults where much of the resistance is due to the ETT which also ses the highest flow rates (Damanhuri et al., 2014). For this reason, resistance values shown in Table 7.5 are all relatively small or effectively zero. This R_{rs} = 0, result may also be due, in part, to the assumed ETT length. A shorter length than assumed, if used, would have lower ΔP_{ETT} and thus it would capture lower resistance pressure drops. Equally, the Jarreau

equation approximation used in ΔP_{ETT} could be too large in some cases (Docherty et al., 2011). However, as R_{rs} is constrained to change more slowly than elastance, it does not significantly affect trends in E_{rs}.

7.4.3 Subgroup Analyses

Patients who received surfactant treatment had lower specific elastance (99% CI difference in medians: -0.49 [-0.48 -0.48] cmH_2O.kg/ml) compared to those that did not (Patients 5 & 8 vs Patients 2, 3, 4, 6, 7, 9, & 10) with p $\leq$ 0.01. This result matches expected behaviour. In particular, surfactant lowers the surface tension, thus lowering the pressure required to keep alveoli and airways open (Wood and Jobe, 1993; Yuksel et al., 1993; JM et al., 1988).

Elastance decreased with increasing patient weight. This result reflects the fact all patients are receiving similar PEEP levels with similar driving pressure. Therefore, increases in tidal volume with increasing in weight, would decrease elastance and thus, this result is expected (Kannangara et al., 2018). Equally, the more premature the infant, the less developed the lung (Greenspan et al., 1988; Liggins et al., 1972), with lack of surfactant production and fewer underdeveloped alveoli (Hislop et al., 1986), and an overall lower weight. Thus, the model effectively captures this expected physiological difference, as desired, demonstrating its ability to assess underlying pulmonary mechanics in this cohort.

7.4.4 Elastance and Resistance Comparison to Literature

Bhutani et al. (1988) used the single compartment model to fit specific compliance to data from 22 neonates (Bhutani et al., 1988). The specific compliance median IQR for Bhutani et al. (1988) was 0.40 [0.34 - 0.57] ml/cmH_2O/kg (Bhutani et al., 1988). The specific compliance median IQR for this study was 0.61 [0.42 - 0.95] ml/cmH_2O/kg. The median and range of IQR for specific compliance for this study is slightly higher than the results

from Bhutani et al. (1988), of the same order of magnitude with overlapping ranges.

There are several different factors that may cause the slightly higher results in this study. Bhutani et al. (1988), performed their analyses in 1988 using external pneumotachometer and pressure transducer, and size of the data was limited to 20-40 breaths per patient in comparison to this study, where ventilator data was retrieved with 20,000 breaths per patient in this study. Patient weight is higher in Bhutani et al. (1988), with lowest weight being 1.51 kg, in comparison to 0.81 kg in this study, so per our results in Figure 7.5, this lower elastance for the Bhutani et al. (1988) cohort is expected. Other factors such as respiratory rate and ventilator mode also differed.

7.4.5 Limitations

This study has small patient numbers (n=9), but very large numbers of recorded breaths (535,428 breaths). After removing asynchronies from all potential cases, 422,475 (79%) breaths were successfully fit using the single compartment model with ETT compensation term (Equation 1). Overall, the results indicate the model captures fundamental, underlying patient-specific elastance and resistance within these limitations.

The results from subgroup analysis also provide preliminary indication the model captures expected physiological and clinical outcomes and trends. This latter point is critical for any model used in clinical monitoring or care. This is a proof of concept study to apply model-based method to clinical infant data to assess underlying pulmonary mechanics and therefore the small number of patients was deemed less important than the very large number of breaths (422,475) captured for analysis.

Patients underwent different recording period lengths for clinical and technical reasons, and so varying numbers of breaths were used in the analyses for each patient. However, given the minimum number of breaths used per patient is 10,000 breaths,

there is sufficient data for this analyses. Comparing different subgroups with widely different number of breaths does not change the results either, as a minimum of 60,000 breaths were present per subgroup, and elastance values were not observed to shift significantly over time (Table 5) when compared to subgroup differences.

7.4.6 Comparison to Adult MV

Compared to elastance values of adult ICU patients (Chiew et al., 2011, 2015c), neonates have significantly higher elastance. This result confirms neonates cannot be treated like small adults in managing MV. It also suggests they have differences in lung mechanics (Chakson et al., 2017). However, the underlying model appears to translate cohorts well, implying the underlying mechanical behaviours are similar, even if the specific mechanics values vary. In particular, neonates have a high spontaneous breathing or clinical interaction affecting breaths (21%). Infants also have high intra- and inter- patient variability. Such behaviour is different in comparison to adults as adult ICU patients are sedated (Chase et al., 2004; Wøien et al., 2012; Patel and Kress, 2012; Luks, 2013; de Wit et al., 2009).

7.4.7 Future Work

Future work is required to use model-based method to capture patient-specific lung mechanics in NICU clinical settings in real time. CURE Soft (Szlavecz et al., 2014) allows monitoring of patient-specific lung mechanics in adult ICU in real time. CURE Soft can be modified to be used in NICU settings. 21% of the data were considered as asynchronous or severe spontaneous breathing effort. In adult patients, methods such as pressure reconstruction, allows adjusting asynchronous or spontaneous breath and be able to quantify them (Chiew et al., 2018). Therefore, these methods can be implemented be able to apply model-based methods using the single compartment model to approach neonatal MV.

7.5 Summary

The work performed in this chapter is the first in-depth (535,428 breath) study of NICU pulmonary mechanic quantifying neonatal elastance. The results shows unique behaviours including large inter- and intra- and breath-to-breath patient variability. This study also shows there is significantly greater than expected asynchrony rate of 21%, where there are no prior reparts to compare to. This model was further validated by comparing the sub-cohorts with known differences in elastance, as well as comparison to adults and another NICU study. Technically, the model fit was good and captured the respiratory mechanics well in this cohort using ΔP_{ETT} term.

CHAPTER 8

Pulmonary Sex Differences in Neonates

8.1 Introduction

Newborn male infants have a higher incidence of RDS, morbidity, and mortality than females at similar birth weight (Miller and Futrakul, 1968; Torday et al., 1981). In utero, male foetuses are less developed than females at the same gestational age by 1.5-2 weeks 3 (Torday and Nielsen, 1987). Thus, premature male infants produce less surfactant in comparison, and are more likely to receive invasive MV (Stevenson et al., 2000). Anecdotally, male infants are harder to ventilate, but no studies have yet quantified any differences in lung stiffness or mechanics to support this observation.

It is well documented, model-based methods can be used to identify patient-specific lung mechanics (Chiew et al., 2015c; Bhutani et al., 1988; Chiew et al., 2011; Kim et al., 2019a) and enable better understanding of patient specific condition using existing bedside

measurements. A simple model comprising of a single compartment has been used to describe lung mechanics in adults (Bates, 2009; Chiew et al., 2011, 2015c) and is currently used in a MV trial to guide PEEP selection (Chiew et al., 2015c). In this model, the lungs are treated as a single volume expanding against a spring-stiffness with pressure losses in the airways due to flow resistance. This model has also been applied to retrospective neonatal MV data to describe lung elastance and its differences between infants and changes over time (Kim et al., 2019a).

This chapter analyses MV data to quantify patient-specific elastance, and inter- and intra- patient variability between male and female neonates. The model is fit to clinical data from 9 NICU infants of varying prematurity and condition who were invasively ventilated. Specific elastance is used to factor out weight and size, thus allowing fairer comparison between infants of different maturities. Male infants have stiffer lungs (Carey et al., 2007) and are thus hypothesized to have higher model-based elastance and lower intra-patient variability. This analysis of specific elastance and its variability aims to provide further insight on differences in response between sexes in NICU MV, as well as quantifying the incidence and the level of asynchrony in this cohort for the first time. Both outcomes will provide significant real clinical insight.

8.2 Methods

8.2.1 Patient Data and Acquisition

Mechanically ventilated infant airway pressure and flow data described in Section 3.1 is used in this chapter. A total of 10 infants were ventilated using conventional ventilation mode (CV) or high frequency oscillatory ventilation mode (HFOV), or both. In this cohort, 6 of 10 patients are female infants and other 4 are male infants, where 1 female will be excluded as they were only ventilated using HFOV. In this chapter, the NICU pulmonary mechanics of male and female infants are compared to verify and quantify anecdotal

sex difference characteristics.

8.2.2 Model Fitting

The single compartment model described in Section 2.2, Eq (2.3) and also used in Chapter 7 Eq (7.1) is used in this Chapter. This equation is repeated for ease of reading:

$$P_{aw} = E_{rs}V + R_{rs}Q + PEEP + \Delta P_{ETT} \tag{8.1}$$

Where, P_{aw} is the airway pressure, E_{rs} is the elastance, V is the volume, R_{rs} is the airway resistance, Q is the flow, $PEEP$ is the pressure offset, and ΔP_{ETT} is the pressure loss across the ETT, specifically defined in Chapter 2, Eq (2.9).

The NICU patient cohort has varying weight as it was an observational study and preterm neonate can vary from 500-2000g in weight. This variability range is far larger than seen in other, older and more commonly studied cohort. Thus, specific elastance is utilised to compare NICU pulmonary mechanics as it allows direct comparison (Kannangara et al., 2016b; Kim et al., 2019b). The specific elastance is described in Chapter 7 Eq (7.3) and is repeated here:

$$E_{specific} = E_{rs} * m \tag{8.2}$$

Where, $E_{specific}$ is the specific elastance, E_{rs} is lung elastance and m is the mass of the infant.

8.2.3 Male Infants vs Female Infants

Specific elastance based on infant weight is used to account for patient weight as a marker for maturity. It is useful when comparing infants with large variations in weight as larger infants typically have larger (and more developed) lungs. Larger lung volumes result in different apparent elastances for a given underlying tissue stiffness (Brown and DiBlasi, 2011; Kim et al., 2019a). Specific elastance ($E_{specific}$) is the reciprocal of specific

compliance, which is a metric used to measure the intrinsic elasticity of the lung tissue independent of lung volume, as previously described (Kannangara et al., 2018; Kim et al., 2019a).

In this study, specific elastance ($E_{specific}$) and airway resistance (R_{rs}) are compared in male and female infants. Females are hypothesised to have lower specific elastance as male infants are typically sicker and less developed (Stocks et al., 2007; Torday et al., 1981; Torday and Nielsen, 1987). Resistance is hypothesised to be similar between males and females.

8.2.4 Variability Analysis and Comparison

Preliminary analysis showed large variability between and within patients. This large underlying inter- and intra- patient variability is quantified using percentage difference in breath to breath specific elastance ($\%\Delta E$). The percentage difference in elastance is determined by current specific elastance (current breath, $E_{specific}(N)$) and forward specific elastance (next breath, $E_{specific}(N+1)$), defined:

$$\%\Delta E = \frac{E_{specific}(N) - E_{specific}(N+1)}{E_{specific}(N+1)} \times 100 \tag{8.3}$$

The standard box plot is used to show the overall distribution of specific elastance and its variability for each patient. This plot clearly compares patients and sexes by overall distribution.

The variability in the cohorts of male and female infants is quantified. It is hypothesised male neonates will have much lower intra- and inter- patient variability, as stiffer lungs are harder to inflate and less responsive to small changes in flow-volume input. Overall variability is calculated using the interquartile range (IQR; 75th-25th) of specific elastance and its percentage change over the distribution. As an indication of the relative

size of the variability between patients, the IQR is also divided by the median.

8.2.5 Asynchrony

Ventilator asynchrony occurs when the particular ventilator mode and settings do not match patient breathing efforts. High incidence of ventilator asynchrony can lead prolonged MV duration (Thille et al., 2006, 2008; Chao et al., 1997; Epstein, 2011). There is thus significant value in quantifying the incidence of asynchrony in this cohort.

The level of incidence of patient ventilator asynchrony was quantified, and the percent asynchronous breaths calculated per patient. Asynchrony incidence is compared between male and female infants. The purpose of this comparison is to show the level of patient-ventilator interaction obtained, while comparing the differences due to sex. This result also gives more context to how a patient is responding to MV.

8.2.6 Statistical Comparisons

Statistical comparisons for specific elastance and resistance are made using non-parametric statistics due to non-Gaussian distributions and large data sets (422,475 breaths) (Motulsky, 1995). To assess the overall central tendency of behaviour we analyse the 90% range of results for each infant. Bootstrapping medians was used as the most robust and fundamental means of evaluating statistical comparisons 27, Avoiding the problem of unrealistically low p-values can arise when data sets used in more traditional comparison tests are very large ($N > 10{,}000$) (Motulsky, 2015).

Bootstrapping compared medians from 10,000 breaths with replacement, repeated 10,000 times. A 99% Confidence Interval (CI) for difference in median specific elastance values are created. If the CI does not cross zero, differences in medians are statistically significant with $p \leq 0.01$. This choice of p value significance was made to be more conservative than $p \leq 0.05$, because of multiple comparisons (Motulsky, 2015).

8.3 Results

8.3.1 Male Infants vs Female Infants

Patient clinical data are shown in Chapter 3 Table 3.1. Male infants had higher specific elastance compared to females, as seen in Figure 8.1 and Table 8.1. The median [IQR] of specific elastance for male infants was 1.91[1.33-2.48] $cmH_2O.kg/ml$ and higher than female infants at 1.31[0.86-2.02] $cmH_2O.kg/ml$ ($p<0.01$). The median [IQR] resistance was 0.00[0.00-0.02] and 0.02[0-0.05] cmH_2Os/ml for males and females, respectively ($p<0.01$).

The higher elastance in males matches the hypothesis as male infants are anecdotally harder to ventilate (Stocks et al., 2007). The difference in resistance, while statistically significant, is not likely clinically significant. Equally, it could reflect increased resistance in more developed lung structures with a greater number of branches and alveoli, if female infants are more developed in comparison to males.

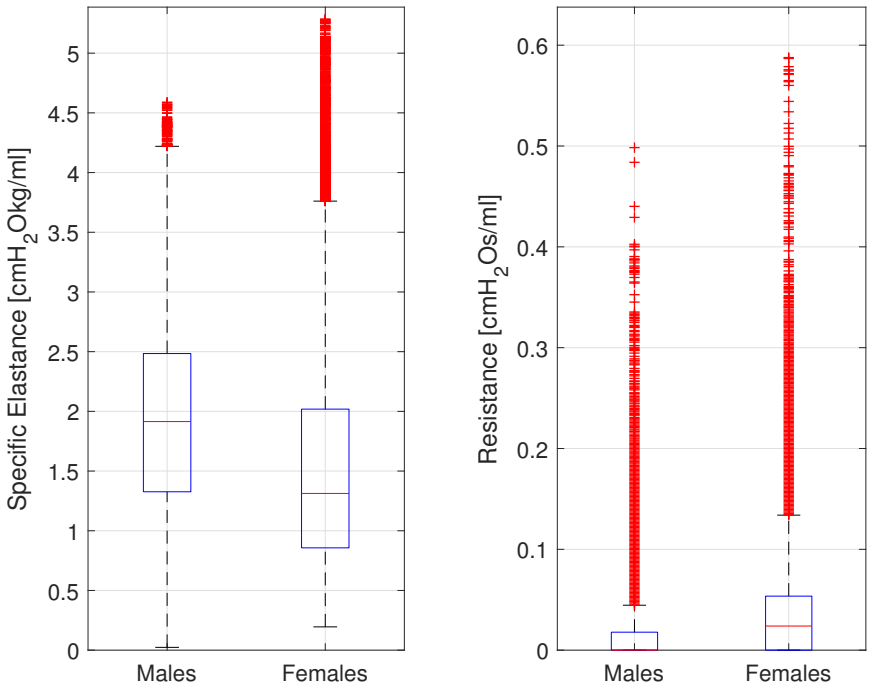

Figure 8.1: Box plot of specific elastance ($E_{specific}$) and resistance (R_{rs}) of sex cohorts. Males have higher $E_{specific}$ ($P < 0.01$) and R_{rs}.

Table 8.1: Median [IQR] of specific elastance, percentage difference in specific elastance ($\%\Delta E$) and the IQR range (75^{th} – 25^{th}). Males are bold face for comparison to females. The hours of recording is also shown.

Patient #	Sex	Hours of Recording	Median [IQR] $E_{specific}$ [cmH_2O/ml/kg]	IQR Range of $E_{specific}$ 75^{th} – 25^{th} [cmH_2O/ml/kg]	IQR Range of $E_{specific}$/median	Median [IQR] $\%\Delta E$ [%]	IQR range of $\%\Delta E$ [%]
2	F	5	0.86 [0.57 - 1.70]	1.13	1.32	-1.60 [-17.83 - 16.16]	33.99
3	**M**	**21**	**0.50 [0.36 - 0.72]**	**0.36**	**0.74**	**-1.45 [-29.84 - 38.13]**	**67.97**
4	F	19.3	1.12 [0.69 - 1.86]	1.17	1.05	-0.88 [-14.40 - 15.11]	29.51
5	F	8.2	0.67 [0.59 - 0.82]	0.23	0.35	-0.31 [-11.55 - 12.61]	24.16
6	**M**	**21**	**2.53 [2.24 - 2.97]**	**0.73**	**0.29**	**-0.05 [-5.33 - 5.63]**	**10.96**
7	F	23.6	2.07 [1.46 - 2.59]	1.13	0.55	-0.54 [-10.58 - 10.36]	20.94
8	F	22	1.29 [1.01 - 1.72]	0.71	0.55	-0.47 [-12.99 - 13.55]	26.54
9	**M**	**24.6**	**2.28 [1.84 - 2.57]**	**0.73**	**0.32**	**-0.02 [-9.53 - 9.65]**	**19.18**
10	**M**	**42.8**	**1.43 [1.17 - 1.65]**	**0.48**	**0.34**	**0.07 [-6.60 - 7.24]**	**13.84**
All*		187.5	1.65 [1.08 - 2.37]	1.29	0.77	-0.20[-9.40 - 9.63]	19.03
Males*			**1.91 [1.33 - 2.48]**	**1.15**	**0.60**	**-0.03 [-7.56 - 8.01]**	**15.57**
Females*			1.31 [0.86 - 2.02]	1.16	0.89	-0.59[-12.56 - 12.86]	25.42

*These categories are weighted by the contributing number of breaths from each patient.

8.3.2 Variability

Variability within and between patients is large. The median [IQR] for specific elastance and breath-to-breath $\%\Delta E$ of each patient and sex is shown in Table 8.1. The median [IQR] of breath-to-breath $\%\Delta E$ across all patients is -0.20[-9.40 - 9.63]%, with absolute IQR range of 19.03% indicating a progression towards lower elastance over time. The minimum per-patient IQR range is 10.96% and the maximum is 67.97%, showing large intra-patient variability, as well as large inter-patient variability in this metric.

Figure 8.2 shows box plots of specific elastance for all patients. Figure 8.2 and Table 8.1 show Patient 3 has the lowest median specific elastance while Patient 5 has the narrowest IQR range for specific elastance as seen in Figure 8.2 but Patient 6 has the lowest IQR range/Median($E_{specific}$). The per-patient IQR range as a percentage of the median value (IQR Range/Median($E_{specific}$)) also varies considerably.

Figure 8.1 and Table 8.1 also show males have consistently higher specific elastance than females, barring male Patient 3 who was near term and relatively large. They also show the hypothesized lower intra- patient variability for males versus females, seen in narrower IQR boxes in Figure 8.2 and values in Table 8.1. Excepting again Patient 3, the same outcome holds for the IQR range of $\%\Delta E$, breath-to-breath.

Figure 8.3 plots median specific elastance against the IQR range of $\%\Delta E$) per patient, assessing breath-to-breath variability as a function of specific elastance. This plot shows a hyperbolic relationship with R^2 = 0.73. Eliminating the outlier at (0.5, 68%; Patient 3 [male]) changes to R^2 = 0.71 so the relationship is robust at this level of correlation. This relationship shows the median specific elastance and IQR range of breath-to-breath $\%\Delta E$) per patient are strongly related. It also shows as median specific elastance rises, breath-to-breath ($\%\Delta E$) variability falls, as hypothesised. This plot shows variability in

a function of $E_{specific}$, not sex. It just happens males have higher $E_{specific}$ per the other results and hypothesis.

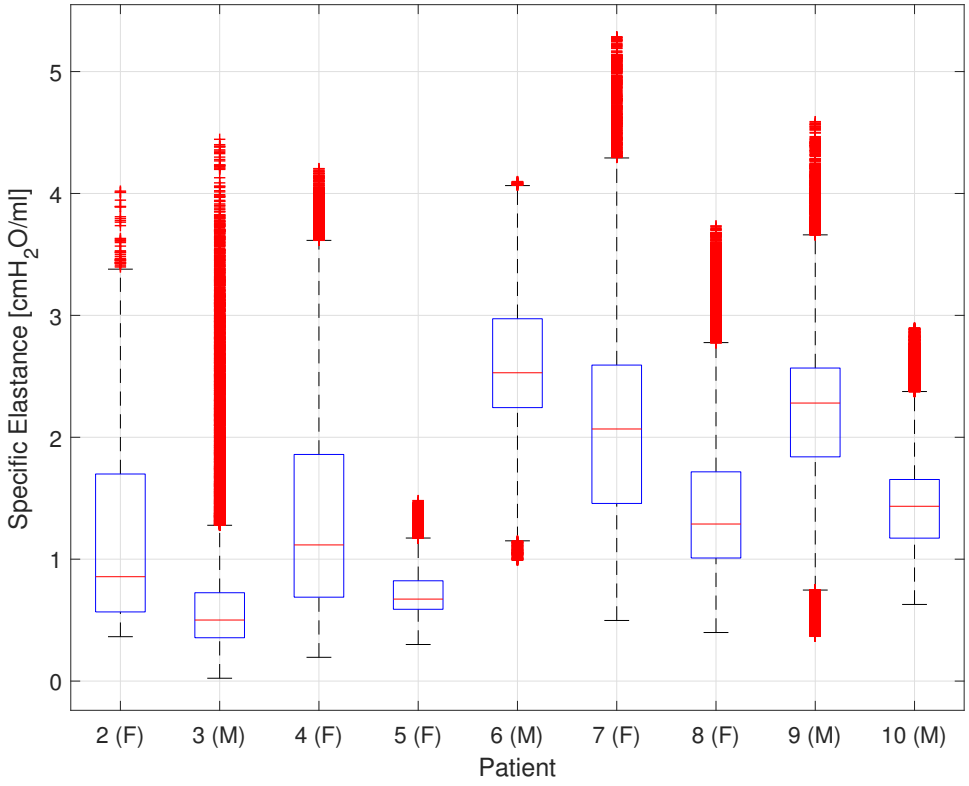

Figure 8.2: Box plot of specific elastance for all patients. Where males (M) and females (F) are denoted on x-axis.

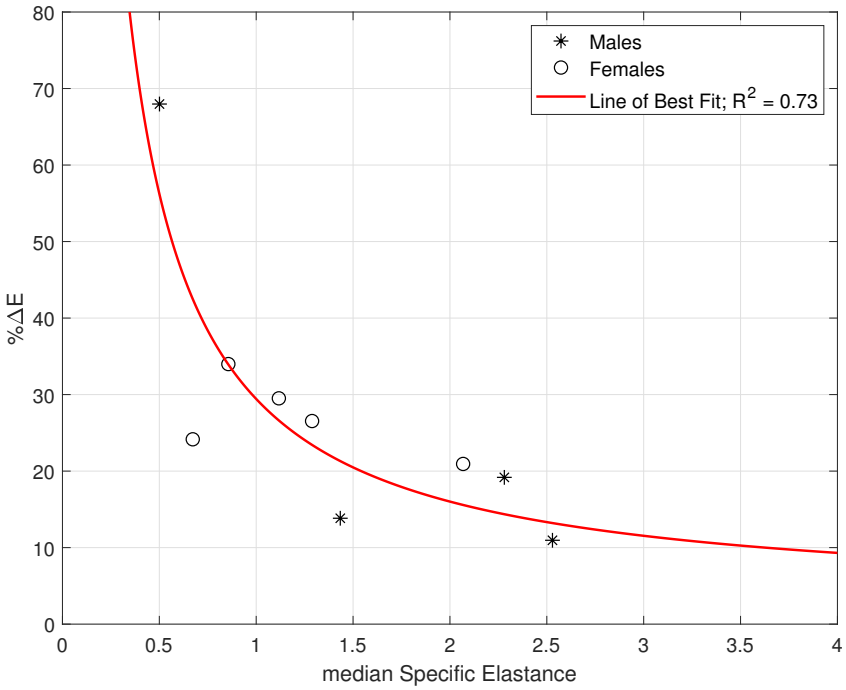

Figure 8.3: Relationship between median specific elastance and IQR range of $\%\Delta E$. A hyperbolic line of best fit is shown in red.

8.3.3 Level of Asynchrony

Asynchronous and outlying breaths were detected. Breaths filtered based on perturbations from a well-accepted model of typical lung dynamics and the relationship between flow-volume and pressure. These breaths total up to 112953 (21%) of the total 535428 breaths.

The percentage asynchrony per patient is shown in Table 8.2. Patient 3 was highly asynchronous. This high level of asynchrony may be a function of his clinical diagnoses (seizures) or the fact he was ventilated using SIMV mode, whereas other patients were on PTV. Male infants (excluding Patient 3) have lower incidence of asynchrony in comparison to female infants, although this is not likely to be statistically significant. The chi-squared test to assess significance is inappropriate here because large data sets results in p = 0 and the patient cohort is too small to bootstrap test (Motulsky, 2015). Patient 6 had lowest occurrence of ventilator asynchrony with 11.24% and Patient 4 had the largest asynchrony with 19.13%.

Table 8.2: Percentage Asynchrony occurrence per patient.

Males		Females	
Patient #	Asynchrony (%)	Patient #	Asynchrony (%)
3	60.74	2	23.44
6	11.24	4	19.13
9	17.24	5	18.17
10	15.29	7	15.58
		8	16.75
Weighted mean	23.65	**Weighted mean**	**17.54**
	14.75*		

*Percentage asynchrony for male infants not accounting for Patient 3

8.4 Discussion

8.4.1 Specific Elastance

Males have higher specific elastance compared to females ($p \leq 0.01$). This behaviour matches the hypothesis, and is supported by anecdotal and literature evidence male infants are harder to ventilate and tend to have longer ventilation period compared to females (Deulofeut et al., 2007; Torday et al., 1981). Thus, a single compartment model is able to quantify established trends, and capture MV behaviour in neonates. Patient 3 was an outlier, in they were male with the lowest overall elastance. However, it was a full-term infant with weight of 3400g, and is likely more mature in terms of lung structure and function. This infant was also ventilated for reasons unrelated to lung function due to severe hypoxic ischemic encephalopathy. Overall, these results match observations male premature infants are less developed with stiffer lungs (Carey et al., 2007; Torday and Nielsen, 1987), which may require a different approach to MV for this cohort.

The results show an initial finding male infants have stiffer lungs, creating a hypothesis for a larger, more controlled study and thus, feels the result of this study would still

hold true for larger and more controlled studies recruiting only pre-term infants with similar weight and gestational age. In particular, such a study would exclude Patient 3 who was near term and much larger, but also reduced the apparent sex differences seen. Therefore, based on these results, a larger controlled study would deliver the same differences with greater statistical power.

8.4.2 Variability

There was large intra- and inter- patient variability observed across the cohort. The lowest breath-to-breath IQR range of the percentage change in elastance ($\%\Delta E$) was 11%, and highest was 68%. The overall elastance distribution of breath-to-breath $\%\Delta E$ varied. Breath-to-breath variability can differ significantly. Patient-specific elastance changes hourly, and breath-to-breath changes can be relatively large (Kim et al., 2019b).

The results show male infants have higher specific elastance, but lower variability, as seen in the IQR range of $E_{specific}$ and breath-to-breath $\%\Delta E$. Excluding the more mature Patient 3, males have significantly lower IQR range/median values compared to female neonates (Table 8.1). This outcome is expected as male infants have higher elastance in the results, excepting Patient 3. Figure 8.3 indicates variability in elastance in a function of median elastance, rather than sex. This result makes sense as higher elastance means stiffer lungs, which are thus less responsive to pressure-flow inputs compared to lungs with lower elastance, and thus less likely to vary given similar ventilator settings.

In Figure 8.3, the hyperbola shape is chosen because this line does not cross zero, thus making physical sense. The correlation of determination (R^2 = 0.73) value does not change much if the outlying first data point is removed. It overall suggests variability is primarily a function of median specific elastance. Such large distributions in variability across the patients shows the potential need to change MV modes more frequently. Equally, it may show a need for better MV modes to account for patient variability in

the NICU environment.

8.4.3 Asynchrony

A total of 112,953 (21%) of breaths were counted as either asynchronous or significantly outlying using the method in Figure 7.1 in Chapter 7 and are not representative of typical MV supported breaths. These 21% of breaths are either asynchronous, or breaths with relatively very large spontaneous breathing efforts, resulting in extreme elastance values or poor model fit to a well-accepted model. Infants are not cuffed or sedated during MV, although morphine is given, which has sedative effects (Chase et al., 2004). Therefore, neonates are more likely prone to ventilator asynchrony.

Patient-ventilator asynchrony severely interferes with MV and is associated with prolonged MV duration and reduced outcomes in adult cohorts (Newberry et al., 2016; Chiew et al., 2018; Gutierrez et al., 2011; Thille et al., 2006; Chao et al., 1997; Epstein, 2011), but has not been studied in NICU cohorts. For this reason, it can be much harder to detect and/or reduce ventilator asynchrony in the NICU setting in comparison to adult ICU (Chiew et al., 2018; Thille et al., 2006). Neonates may thus require much closer and more frequent attention to ventilator settings and response for this reason, as well to minimise asynchrony and further enhance patient-ventilator interaction.

Not accounting for Patient 3, who was solely on SIMV mode, male neonates have lower asynchrony rates. The remaining male and female infants all shared similar ventilator modes, settings, and approach, as per standard care. However, given females had much higher ventilator asynchrony incidence, they may require different ventilator settings than males for this reason, as well as due to differences in lung mechanics and variability.

8.4.4 Overview and Clinical Implications

This analysis used specific elastance, a measure which accounts for patient weight Kannangara et al. (2016b). Other studies indicate lung development and volume are strongly associated with weight (Brown and DiBlasi, 2011; Kim et al., 2019a). However, the high variability between patients seen here is also likely a function of infant injury or disease state and associated complications. Males were seen to have higher elastance and less variability overall and breath-to-breath.

These results suggest MV management for infant males should be different to infant females as male neonates have stiffer lungs and are thus less variable in response to MV. They may also pose a greater risk for over inflation (barotrauma) or under recruitment/oxygenation. In contrast female neonates showed greater variability associated with lower specific elastance, and thus may likely need more frequent observation and/or changes in MV settings.

The identified resistance values for the model are very low due to the ΔP_{ETT} term added to the model and used in this analysis. The ETT is the single largest resistor in patient breathing. This term thus captures most of the flow resistance behaviour observed in the data. Calculating it separately, as in this analysis, leaves relatively little further flow resistance to be identified from the model term. Therefore, the (added) identified airway resistance, R_{rs}, is relatively low. Clinically, it implies a need to account specifically for ETT length, as well as noting there is less need to specifically focus on resistive losses in this cohort.

8.4.5 Limitations

The major limitation of this study is small patient numbers (n= 9). However, the number of recorded breaths are large (535,428 breaths). This large number of breaths and the

robust statistics used help ensure the validity of the results for this initial observational cohort. Despite the small patient numbers, the male vs female neonates comparisons showed the hypothesized trends in elastance, which can be further verified in larger studies.

The model itself is relatively simple (Bates, 2009; Ben-Tal, 2006; Chase et al., 2016, 2018; Morton et al., 2019a), and analyses lungs as a combined volumetric unit. It is therefore unable to independently describe differences in MV properties between the lungs or lung units (heterogeneity), but presents an overall average description of their combined behaviour. This model has been successfully applied to adults (Chiew et al., 2011), and has the advantage in it can be easily identified using readily available bedside data with no additional measurements (Docherty et al., 2011; Schranz et al., 2012c; Docherty et al., 2014).

Particular, the single compartment model is structurally simple compared to non-linear models. Non-linear models might be able capture more specific differences and insight in lung mechanics properties. However, such models are far less identifiable and often not practically identifiable (Docherty et al., 2011), meaning unique parameter values may not be able to be found with the clinical data available without invasive and burdensome added procedures or measurements not typically available for this cohort. There is thus a trade-off of ease of use and detail (Chase et al., 2018).

8.5 Summary

In this chapter, the difference between mechanically ventilated male and female infants in terms of specific elastance, inter- and intra- patient variability were studied. Male neonates had higher specific elastance than female neonates. Females had greater intra-patient and breath-to-breath variability, which increased with declining specific elastance. These results indicate male and female infants should be ventilated differ-

ently, where higher variability in females show they may require more frequent observation and changes during MV. In contrast, males may require different ventilation modes and/or settings than females.

CHAPTER 9

Quantifying neonatal patient effort and asynchrony using basis functions

9.1 Introduction

In previous chapters, neonatal pulmonary mechanics are quantified using single compartment mode. Model fit was good, validated by comparing charges to known clinical and physiological trends (Kim et al., 2019a,b). However, the single compartment model is limited because it can not uniquely separate heterogeneity of lung in different regions and can not distinguish asynchrony or spontaneous breathing efforts separate from normal breathing without significant assumptions (Blanch et al., 2015; Georgopoulos et al., 2006; Mellott et al., 2014; Vicario et al., 2016; Blanch et al., 2012; Mulqueeny et al., 2007; Poole et al., 2014; Damanhuri et al., 2016; Chiew et al., 2015b; Major et al., 2016b; Kannan-

gara et al., 2016a; Chiew et al., 2018). This NICU cohort described in Chapter 2, were not sedated during their data recording per standard practice, and thus exhibit spontaneous breathing effort in many to most breaths. These spontaneous breathing efforts cause, large breath-to-breath variability, which in turn, causes difficulty in separating underlying patient lung elastance and patient effort due to identifiability issues (Docherty et al., 2011; Schranz et al., 2012b).

In Chapter 5, new method has been developed at separating patient lung mechanics and patient spontaneous breathing effort in adults on NAVA ventilation. In this chapter, the same approach is made to segregate patient lung mechanics, patient inspiratory effort and asynchrony in the NICU cohort. The single compartment model is modified to incorporate basis functions and dynamic lung elastance (Morton et al., 2019b; Chiew et al., 2015a). The two basis functions capture recruitment and distension, and the dynamic elastance captures both inspiratory effort and asynchrony. Basis functions are a form of regularisation, defining normal breathing dynamics, where the remainder or error must be attributable to other courses based on timing and dynamic effect. The aim is to quantify apparent or estimated inspiratory effort relative to an established model of lung recruitment.

9.2 Methods

9.2.1 Patient Data and Acquisition

MV data from 10 invasively mechanically ventilated patients described in Section 3.1 is used in this chapter. Only the patients ventilated using conventional ventilation (CV) mode are examined in this chapter as high frequency oscillatory ventilation (HFOV) mode does not exhibit normal typical breathing.

In this chapter, the first hour recording for each patient on CV is used to determine basis

function model fit and validate the method presented to quantify patient effort. Only the first hour of each patient is used as it allows a more consistent number of breaths per patient, due to differences in recording periods. At roughly 3600 breath per hour, there are enough data points to validate this method. See Table 3.1 for patient demographics.

9.2.2 Model Fitting

A linear single compartment model using Jarreau's equation for pressure loss across the endotracheal tube (ETT) described in Section 2.2, Eq (2.3) and also used in Chapter 7 Eq (7.1) and Chapter 8 Eq (8.1) is used to estimate patient-specific lung condition (Bates, 2009; Chiew et al., 2011; Jarreau et al., 1999; Kim et al., 2019a,b, 2017). This equation has been successfully implemented in NICU cohorts (Kim et al., 2019a,b) as described in Chapters 7 and 8. This equation is repeated in this chapter for clarity:

$$P_{aw} = E_{rs}V + R_{rs}Q + PEEP + \Delta P_{ETT} \tag{9.1}$$

Where, P_{aw} is the airway pressure [cmH_2O], E_{rs} is the elastance of the lung [cmH_2O/ml], V is the volume [ml], R_{rs} is the airway resistance [cmH_2Os/ml], Q is the flow [ml/s], $PEEP$ is the pressure offset [cmH_2O], and ΔP_{ETT} is the pressure loss across the ETT [cmH_2O], specifically defined in Chapter 2, Eq (2.9).

The single compartment model from Eq (9.1) is modified using basis functions described in Section 2.3 to describe the alveoli recruitment Φ_1 and distension Φ_2 (Morton et al., 2019b,a). These basis functions and similar approaches have previously been used in adult critical models (Langdon et al., 2017; Morton et al., 2019b,a). For NICU infants, these functions are defined over a tidal volume range of 0-14ml and pressure ranges 0-60 cmH_2O, which covers all likely NICU MV ranges. Figure 9.1 is repeated from Chapter 2 (Figure 2.2) depicting the basis function shapes.

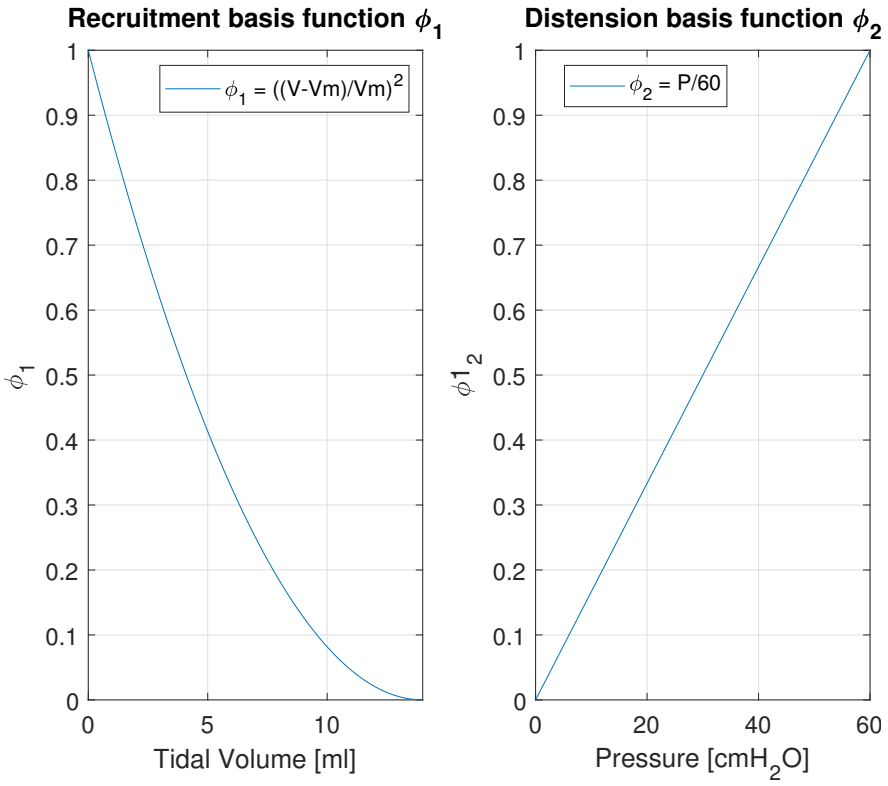

Figure 9.1: Recruitment and distension basis function shapes with volume ranges adjusted for NICU cohort. (Both functions are dimensionless).

The recruitment basis functions is repeated from Chapter 2, Eq (2.4) in this chapter as:

$$\phi_1 = \left(\frac{V - Vm}{Vm}\right)^2 \tag{9.2}$$

Where Vm is the upper limit of 1L in adults and ϕ_1 is set to 0 for $V > Vm$ but the Vm limit is adjusted to 14ml to fit for NICU volume ranges. The 14ml limit should cover all NICU tidal volume ranges as they are typically ventilated at 4-8ml/kg (Brown and DiBlasi, 2011). And the distension basis function is repeated from Chapter 2, Eq (2.5) as:

$$\phi_2 = \frac{P(t)}{60} \tag{9.3}$$

The two basis functions are added to single compartment model, which is also repeated

from Eq (2.6):

$$P_{aw} = E_1\phi 1_1 V + E_2\phi 1_2 V + RQ + PEEP \tag{9.4}$$

As described in Section 2.5, neonates are ventilated at constant low PEEP (< 6 cm_2O) and thus, distension is not identified. In Chapter 8, the resistance term R was near-zero as the ΔP_{ETT} term absorbed most of it. Therefore, these outcomes result in a much simpler equation, which is repeated from Eq (2.12), leaving:

$$P_{aw} = E_1\phi 1_1 V + PEEP + \Delta P_{ETT} \tag{9.5}$$

Neonates in this cohort are not sedated and thus exhibit spontaneous breathing effort. Therefore, as described in Section 2.5, time-varying elastance $Edrs$ is utilised to capture the inspiratory effort (Chiew et al., 2015a). The additional time-varying elastance equation is shown in Eq (2.13) and is repeated here for ease of reading:

$$P_{aw} = Edrs(t) \times V(t) + E_1\phi 1_1 V(t) + PEEP + \Delta P_{ETT} \tag{9.6}$$

Where $Edrs(t)$ is defined:

$$Edrs(t) = \frac{P_{aw}(t) - P_{basismodel}(t)}{V(t)} \tag{9.7}$$

In this formulation, $Edrs(t)$ is the error between expected typical breathing dynamics defined by the basis functions. It thus captures behaviours like spontaneous breathing effort ($Edrs(t) < 0$) and asynchrony ($Edrs(t) > 0$).

First, E_1 using Eq (9.5) is fit and linear least squares regression. Secondly, $Edrs$ is fit using Eq (9.7). It is thus essentially the error after identifying Eq (9.4), using E_1 primarily

due to spontaneous breathing. Taking the area under the curve (AUC) of Edrs results in $AUCEdrs$, an absolute $Edrs$ value can be compared across breaths and patients.

Preliminary study showed there are approximately six common shapes of $Edrs(t)$ as seen in Figure 9.2. The shapes are commonly occurring across patients, where some shapes may have significantly higher occurrence than others. As seen in Figure 9.2, the $Edrs$ values all converge to zero at end inspiration as expected. However, small offset exists where this convergence does not reach zero. Thus, the median of last 25% of the inspiratory Edrs is used to determine the effective zero and mitigate small errors.

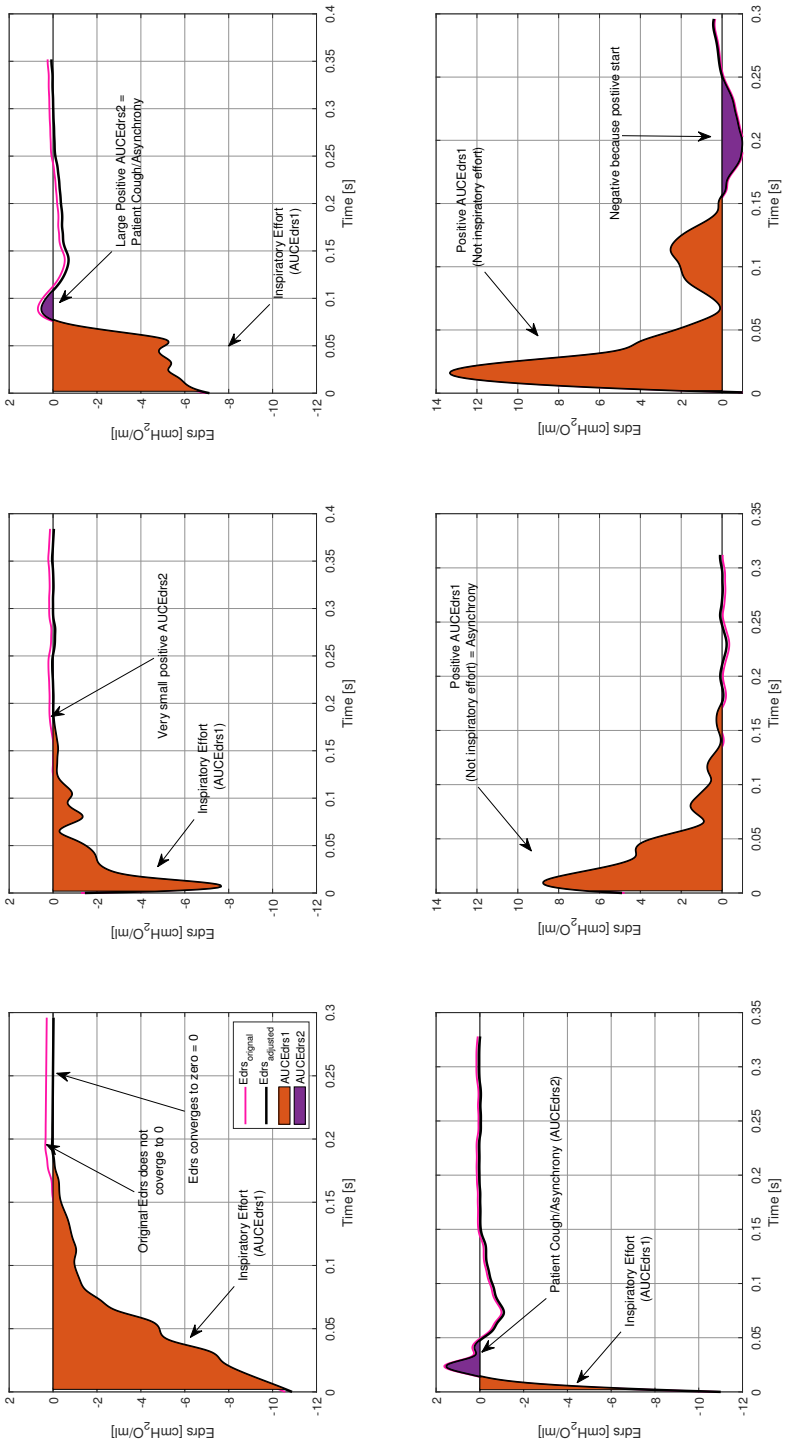

Figure 9.2: Six common $Edrs$ shapes with $Edrs$ original, $Edrs adjusted$, $AUCEdrs1$ and $AUCEdrs2$.

It can be hypothesised: $Edrs$ curves for each breath can be used to describe patient-specific condition and responsiveness to ventilator support. It can be assumed most of the patient-specific inspiratory effort or asynchrony occurs at the start of inspiration. Thus, $Edrs$ is separated into two sections based on the first two occurrence of zero crossing points. The first zero crossing section is mostly patient effort and second zero crossing section is mostly asynchrony. Figure 9.2 shows how each of the common shapes are divided. Note, inspiratory effort can be positive, rather than negative, if the infant is asynchronous or coughs and is thus "fighting" the ventilator applied breath, as also shown in Figure 9.2.

Taking the AUC of the two sections, the patient effort and asynchrony based on the zero crossing is defined. The first section (start to first zero crossing; $AUCEdrs1$ in Figure 9.2) would represents spontaneous breathing effort, and is typically a negative area. The second section (first zero crossing to second; $AUCEdrs2$ in Figure 9.2) represents asynchrony, and its typically a positive area.

9.2.3 Analyses

Model fit, patient effort and asynchrony are assessed and presented as median and [IQR] (interquartile range). The percentage contribution of $AUCEdrs1$, $AUCEdrs2$, and $AUCEdrs$ of rest of the breath are also presented ($AUCEdrs1 + AUCEdrs2 + AUCEdrsrest = 100\%$). The percentage contribution of each component is also shown, as it could provide further insight on the magnitude of each component and its contribution on patient-specific breath.

The patient effort and asynchrony are described by the AUC of $Edrs$. The cumulative distributive function (CDF) plots are used to compare the $AUCEdrs1,2$ across the cohort. The CDF plots on $AUCEdrs1$ would allow visualisation of distribution of $AUCEdrs$ across cohort. If majority of $AUCEdrs1$ are negative, then the $AUCEdrs1$ are properly

capturing patient effort. The CDF plots of $AUCEdrs2$ will show how much asynchronous or coughing-like events occur across the cohort. More specifically, asynchrony causes $Edrs > 0$, while patient effort causes $Edrs < 0$ (Chiew et al., 2015a).

A scatter plot comparing $AUCEdrs1,2$ is used to compare the relationship between the two segments. This plot would show both magnitude and frequency of $AUCEdrs1,2$ values calculated. It will also show the tradeoff between spontaneous breathing effort and asynchrony, where it could be hypothesized strong patient effort obviates asynchrony and asynchrony is likely matched to minimal spontaneous breathing effort. If the model is successful in separating out patient effort and asynchrony, then a large number of data points would be in negative region of $AUCEdrs1$ and positive or near zero for $AUCEdrs2$, and vice versa for asynchronous breaths from Eq (9.6).

9.3 Results

A total of 25,287 breaths from 9 patients were used to fit basis function model. The number of breaths detected, used, and the median [IQR] of basis function identified E_1 from Eq (9.5) is shown in Table 9.1. A total of 187 breaths (0.7%) were removed as distorted breaths, not presentative of typical inspiration and/or expiration using the criteria at Chapter 7 Figure 7.2. The median IQR identified for E_1 is 3.82 [2.09 – 5.80] cmH_2O/ml.

Figure 9.3 shows an example of model fit. It can clearly be seen the $Edrs$ term absorbs the difference between airway pressure and model fit pressure using Eq (9.5), as proposed. $Edrs$ exhibits commonly occurring $Edrs$ shapes, as seen in Figure 9.2, and it converges to zero, as expected.

Table 9.2 shows the median [IQR] of $AUCEdrs1$, $AUCEdrs2$ and the $AUCEdrs$ of the rest of the inspiration. The overall median [IQR] of AUCEdrs1 is -0.32 [-0.43 - -0.12]

Table 9.1: Number of breaths detected and used and Median IQR of E_1.

Patient	Total Breath	Breath used	Breath removed	Median IQR of E_1 [cmH_2O/ml]
2	2227	2211	16	2.24 [1.72 - 3.83]
3	1770	1741	29	1.04 [0.56 - 2.05]
4	1622	1618	4	3.64 [2.57 - 5.07]
5	3582	3547	35	1.79 [1.37 - 2.35]
6	3595	3595	0	6.57 [6.21 - 6.91]
7	2897	2887	10	4.31 [3.08 - 5.88]
8	2796	2787	9	2.39 [2.01 - 3.09]
9	3279	3198	81	4.66 [3.50 - 5.74]
10	3706	3703	3	5.10 [4.30 - 6.19]
Total	**25474**	**25287**	**187**	**3.82 [2.09 - 5.80]**

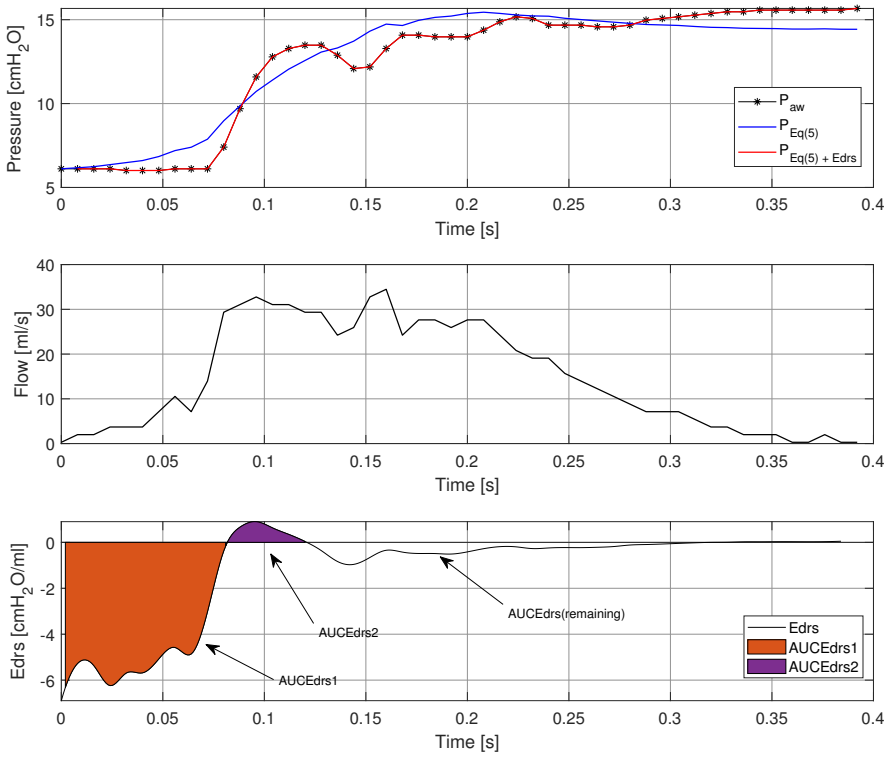

Figure 9.3: example of model fit before and after $Edrs$ is applied Area under curve (AUC) is separated into first, second, and remaining AUC, based on first and second zero crossing points.

cmH_2O/ml and $AUCEdrs2$ is 0.00 [0.00 – 0.01] cmH_2O/ml. The median IQR percentage of all $AUCEdrs$ of each of these first two $Edrs$ sections are 79.24 [64.31 – 85.20]% and 1.41 [0.17 – 13.48]%.

Table 9.2: Median IQR of $AUCEdrs$ and percent contribution of $AUCEdrs$. $AUCEdrs$ is visually depicted in Figure 9.3.

MV	Median IQR $AUCEdrs$ [cmH_2O/ml]			Percent [%] Median IQR		
	$AUCEdrs1$	$AUCEdrs2$	AUC remaining	$AUCEdrs1$	$AUCEdrs2$	AUC remaining
2	-0.35 [-0.41 - -0.18]	0.00 [0.00 - 0.00]	0.09 [0.03 - 0.14]	73.81 [64.63 - 81.66]	0.29 [0.13 - 1.82]	24.94 [16.77 - 32.21]
3	-0.22 [-0.30 - -0.15]	0.01 [0.00 - 0.04]	0.03 [-0.00 - 0.17]	66.04 [51.22 - 84.05]	2.76 [0.23 - 17.48]	16.03 [6.64 - 36.53]
4	-0.47 [-0.64 - -0.35]	0.00 [0.00 - 0.00]	0.43 [0.30 - 0.60]	53.17 [48.09 - 58.70]	0.15 [0.03 - 0.32]	46.06 [40.47 - 51.10]
5	-0.24 [-0.37 - -0.10]	0.00 [0.00 - 0.00]	0.23 [0.17 - 0.29]	46.77 [34.73 - 58.87]	0.28 [0.16 - 0.49]	50.81 [40.41 - 62.12]
6	-0.33 [-0.39 - -0.28]	0.00 [0.00 - 0.00]	0.19 [0.15 - 0.29]	63.69 [52.74 - 68.53]	0.18 [0.05 - 1.12]	35.07 [30.22 - 46.04]
7	-0.32 [-0.45 - -0.06]	0.02 [0.00 - 0.06]	0.09 [0.03 - 0.17]	71.72 [60.71 - 79.02]	4.44 [0.47 - 13.62]	21.57 [12.36 - 29.79]
8	-0.29 [-0.36 - -0.05]	0.00 [0.00 - 0.02]	0.06 [-0.02 - 0.11]	73.10 [59.27 - 80.87]	0.44 [0.10 - 11.47]	23.65 [14.88 - 31.20]
9	-0.11 [-0.35 - -0.03]	0.00 [0.00 - 0.02]	0.07 [-0.02 - 0.20]	57.48 [35.23 - 68.62]	1.17 [0.15 - 17.02]	35.53 [25.10 - 48.06]
10	-0.45 [-0.59 - -0.12]	0.01 [0.00 - 0.05]	0.07 [0.02 - 0.13]	79.24 [64.31 - 85.20]	1.41 [0.17 - 13.48]	16.91 [9.53 - 24.06]
All	-0.32 [-0.43 - -0.12]	0.00 [0.00 - 0.01]	0.13 [0.04 - 0.23]	79.24 [64.31 - 85.20]	1.41 [0.17 - 13.48]	16.91 [9.53 - 24.06]

Figures 9.4 shows the CDFs of $AUCEdrs1$ and $AUCEdrs2$, a scatter plot of $AUCEdrs1$ and $AUCEdrs2$, and example of randomly selected $Edrs$ shapes in range of the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles to show behaviour at each level. Figure 9.4 also shows a zoomed in scatter plot with corresponding percentile positions for Patient 7. The randomly selected $Edrs$ shapes all retain the 'common' shapes shown in Figure 9.2. The zoomed scatter plot shows a pink box representing the 5^{th}-95^{th} range and a yellow box representing the 25^{th} – 75^{th} range. Figure 9.4 shows large negative $AUCEdrs1$ usually has small or negligible $AUCEdrs2$, and large positive $AUCEdrs1$ has small or negligible negative $AUCEdrs2$. Thus, breaths usually either have high inspiratory drive, or are highly asynchronous.

Figures 9.5 show CDF plots of $AUCEdrs1$, $AUCEdrs2$ and scatter plot of $AUCEdrs1$ and $AUCEdrs2$ for Patients 5, 9 and 10. The CDFs of $AUCEdrs1$ show most of $AUCEdrs1$ are negative, as expected, and show clear signs of spontaneous breathing effort. The CDFs of $AUCEdrs2$ show most of the $AUCEdrs2$ values are positive, which implies, they are likely asynchronous events, such as a cough during inspiration, even if small in magnitude. It should be noted 98% (3511/3595 breaths) of $AUCEdrs1$ values for Patient 6 are negative. Patients 6,7, 9, and, 10, seen in Figures 9.4 and 9.5, show a very small percentage of $AUCEdrs2$ are negative, which also indicates asynchrony.

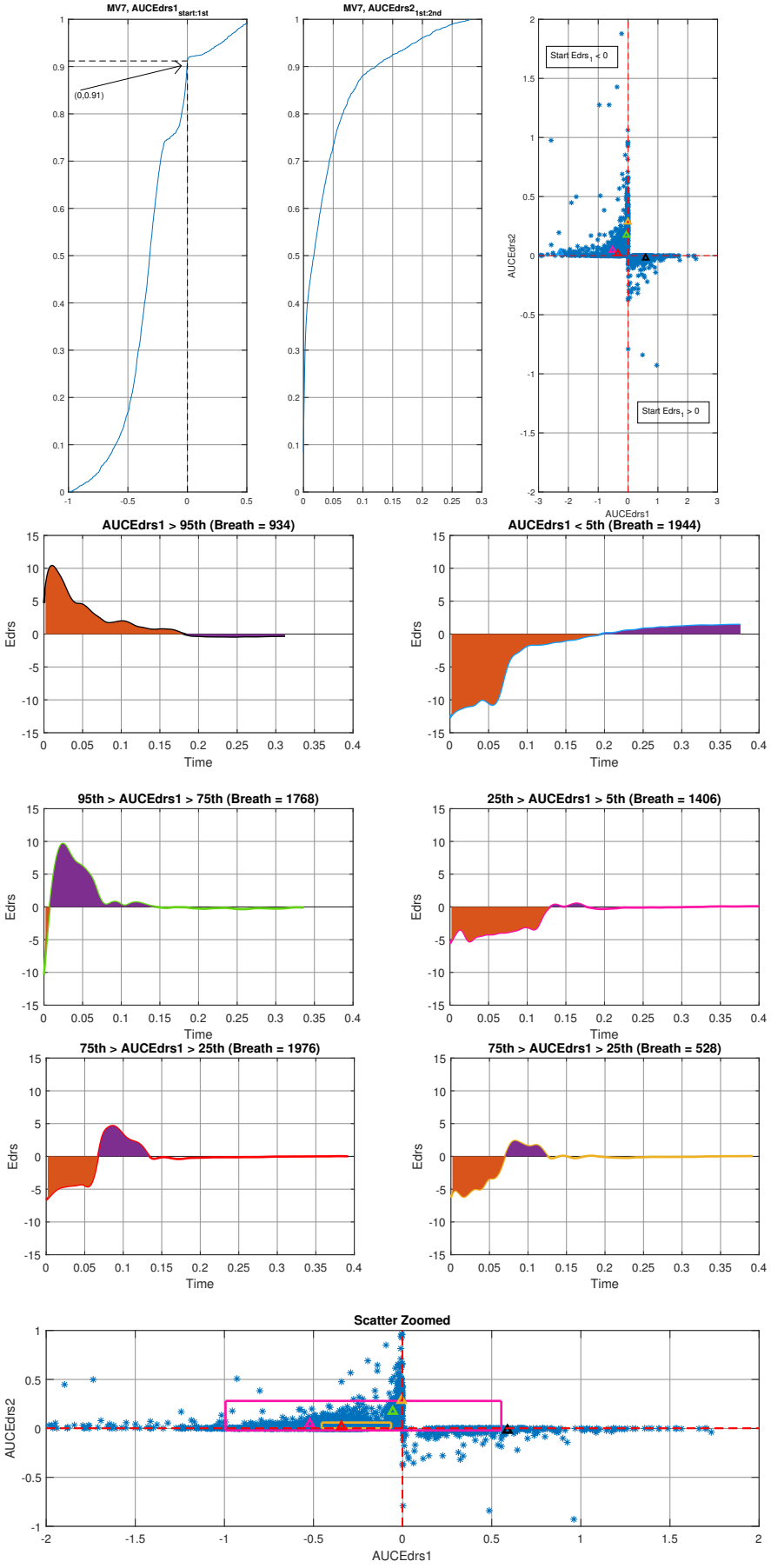

Figure 9.4: CDFs of $AUCEdrs1$ and $AUCEdrs2$, scatter plot of $AUCEdrs1$ and $AUCEdrs2$ and example $Edrs$ curve in range of 5,25,50,75, and 95th percentiles.

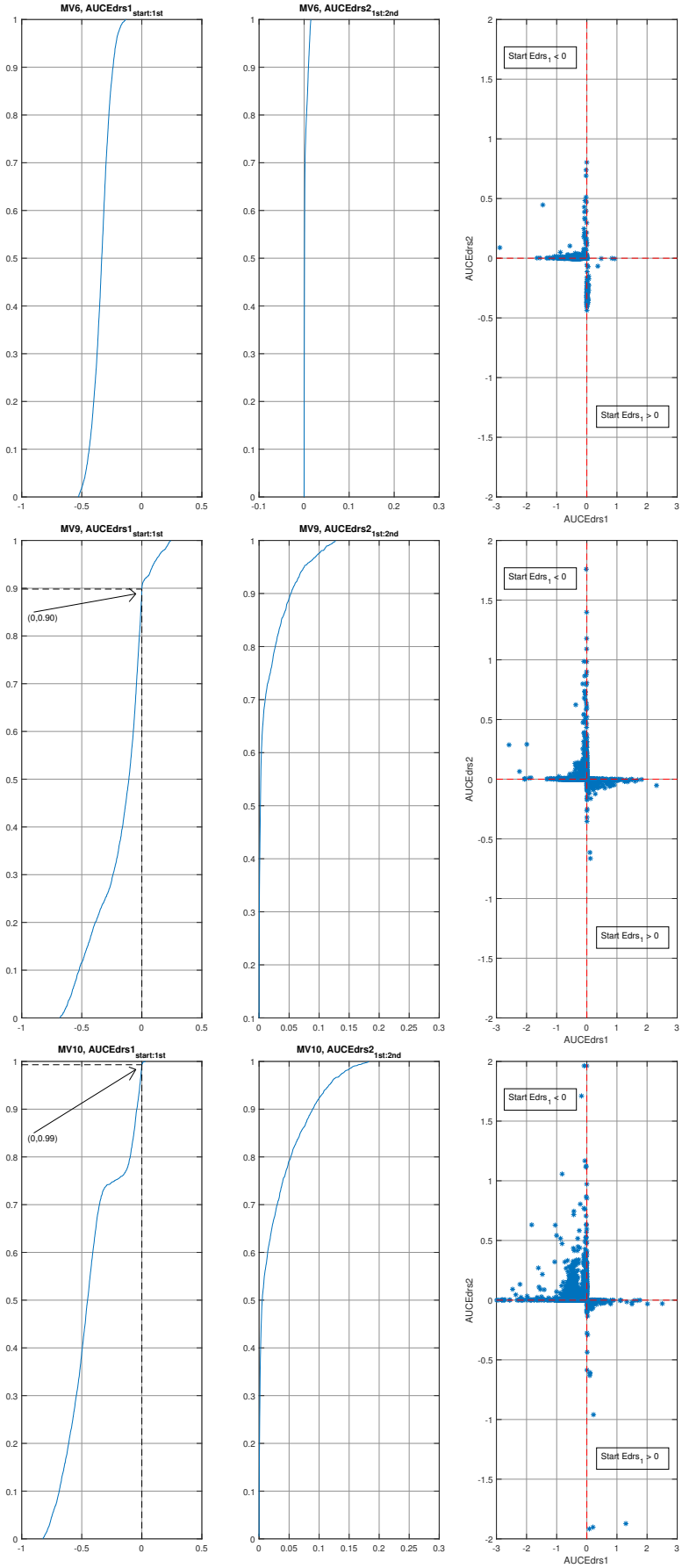

Figure 9.5: CDF plots of $AUCEdrs1$ and $AUCEdrs2$ and scatter of $AUCEdrs1$ and $AUCEdrs2$ for Patients 6, 9, and 10.

9.4 Discussion

The basis functions used here have been previously used to capture patient specific elastance in adult cohorts (Morton et al., 2019a,b) $Edrs$ is intended to quantify spontaneous breathing effort and asynchrony. Overall, it appears $Edrs$ is able to capture these effects, as the shape of $Edrs$ decays to zero over time, as would be expected for breathing effort. The magnitude and shape also match expectations for effort and resistance.

Overall, the recruitment elastance (E_1) for this cohort was 3.82 [2.09 - 5.80] cmH_2O/ml, the patient effort ($AUCEdrs1$) was -0.32 [-0.43 - -0.12] cmH_2O/ml and asynchrony ($AUCEdrs2$) was 0.00 [0.00 – 0.01] cmH_2O/ml. The percentage contribution of spontaneous breathing and asynchrony on a breath was 79.24 [64.31 - 85.20]% and 1.41 [0.17 - 13.48]% across the cohort. Generally, these numbers match anecdotal clinical expectations.

Spontaneous breathing is captured as (un-modelled) negative elastance of the beginning of inspiration with this model (Chiew et al., 2015a). Notably, 91% of $AUCEdrs$ (23070 out of 25287, 91.2%) values were less than zero, implying spontaneous breathing effort. The CDFs in Figure 9.5 show $AUCEdrs1$ have negative occurrences of 90^{th} percentile or higher (Patient 10 was 99^{th} percentile). This outcome is expected in the patient triggered ventilation (PTV) spontaneous breathing mode used. Thus, this MV model allowed assessment of spontaneous breathing effort in this cohort, where the very high percentage of $AUCEdrs1 < 0$ implies it is capturing this effort.

The $Edrs$ parameter is strongly affected during the first 25% of inspiration, where patient effort is greatest. The negative start and typical rise to zero is expected from diminishing patient effort as the lung fills. Thus, the shape and nature of $Edrs$ as used here is capturing a surrogate of physiological, patient-specific and breath-specific inspiratory effort. Therefore, when $Edrs$ starts negative and rises beyond zero to a noticeable posi-

tive peak resulting in $AUCEdrs1 < 0$, it strongly implies spontaneous breathing leading to patient-ventilator asynchrony represented in the positive portion.

Asynchrony was interpreted as positive $Edrs$, implying additional resistance to a ventilator delivered breath, not already captured by the basis functions. Patient 7 has the largest breath asynchrony contribution with 4.44 [0.47 - 13.62]% and had a large IQR range. This result can also be seen in Figure 9.4 of randomly selected $Edrs$ plots, where positive $Edrs$ peaks exist after the first zero crossing. Patient 5 has the lowest contribution of asynchrony with 0.28 [0.16 - 0.49]%, which is likely clinically negligible in impact. These results can also be observed in the CDF plots of Figure 9.5 where Patient 5 has mostly a straight vertical line and Patient 7 is not. These findings suggest Patient 7 was ventilated sub-optimally, as this patient was highly asynchronous in comparison to other patients.

The scatter plots in Figures 9.4 and 9.5, show the relationship between $AUCEdrs1$ and $AUCEdrs2$ for Patients 7, 6, 9, and 10. It shows most of the $AUCEdrs1 < 0$ and most of the $AUCEdrs2 \approx 0$, implying good synchronisation between patient effort and ventilator delivery. Positive $AUCEdrs2$ or $AUCEdrs1$ implies poor synchronisation with the ventilator, resulting in pressure increases across the airway and lungs. Such pressure increases may be dangerous (Hillman and Albin, 1986; Petersen and Baier, 1983; Gammon et al., 1992; Cullen and Caldera, 1979).

AUC $Edrs$ could be used for monitoring patient synchrony with the ventilator, for optimisation of ventilation modes and settings. For example, the 5th-95th range shown in pink, and the 25^{th}-75^{th} range shown in yellow in Figure 9.4 for Patient 7. The scatter plot in Figure 9.4, shows the data points of example $Edrs$ breaths, this plot can be utilised to provide a real-time means of monitoring asynchrony incidence and magnitude, as well as monitoring breathing effort. It is thus a real-time diagnostic, easily enabling

monitoring of patient-ventilator synchrony in real-time, breath-to-breath.

E_1 still follows expected trends across all patients. Patient 3 had the lowest elastance with E_1 of 1.79 [1.37 - 2.35] cmH_2O/ml and Patient 6 had the highest elastance with 6.57 [6.21 - 6.91] cmH_2O/ml. These results are similar to previous work in Chapter 7 Kim et al. (2019a,b). It should be noted Patient 3, who had the lowest elastance, was a near full-term infant and likely most developed patient, so this result matches expectations. Further, this patient was ventilated for reasons unrelated to lung functions implying no additional stiffness of the lungs due to disease or injury. Patient 6 was a male infant with gestational age of 27.4 weeks and given the anecdotal expectation boys are harder to ventilate than girls due to their relative prematurity (Kim et al., 2019b; Peacock et al., 2012; Torday and Nielsen, 1987) and the results in Chapter 8, it was expected this patient would have the highest elastance (Kim et al., 2019a,b). This higher elastance implies one, or a combination, of smaller tidal or recruitment volume, decreased surfactant production, greater illness or injury, or less developed lung structures.

9.5 Limitations

This analysis has small patient numbers (n=9) and only the first hour from each patient are used for ease of visualisation and analysis. However, infants have high respiratory rate (60 breaths/min) and therefore large number of breaths were analysed (25287 breaths). Thus, this proof of concept analysis shows promises in the application of basis function models and $Edrs(t)$ to separate patient-specific lung condition (elastance), spontaneous breathing effort ($AUCEdrs1$) and asynchrony ($AUCEdrs2$).

9.6 Summary

The basis function with Edrs was able to separate patient lung condition, E_1 with spontaneous breathing effort $AUCEdrs1$, and asynchrony $AUCEdrs2$. The recruitment basis

function had overall good fit and captured respiratory mechanics. The $Edrs$ trajectory was able to estimate spontaneous breathing effort and asynchrony and offers a real-time method to track these important MV parameters.

CHAPTER 10

Conclusions

This thesis presents patient-specific elastance modelling and quantification of sedated and spontaneous breathing effort in both adult and neonatal intensive care unit cohorts receiving invasive mechanical ventilation. In both adults and neonates, new approach has been developed to quantify patient spontaneous breathing effort using $Edrs$, a time-varying elastance, and physiologically relevant basis functions. The protocol for CURE RCT is also established and is on-hold for the trial to commence. In neonatal cohorts, the first in-depth analysis of infant lung mechanics and physiology is presented and the unique observed sex differences have been quantified.

There has yet to be a study exploring lung physiology in preterm neonates. Chapter 7 presents the first in-depth analysis for identifying lung elastance in neonates. The single compartment lung model (Bates, 2009) was fit breath-to-breath over 535,428 inspiratory breath. The breaths were identified well and results were further validated by capturing known physiological differences. These results provide the first validation of the ability of this modelling and identification approach extending to very different neonatal

cohorts.

The existence of sex differences in male and female infants is widely known in the field. While there are studies which shows male infants have higher incidence of RDS, mortality and morbidity, these differences have not been quantified at a physiological or lung mechanics level. There are also anecdotal reports male infants are harder to ventilate than female infants, but again these aspects have never been formally observed or quantified. In Chapter 8, specific elastance was compared in male and female infants. Results showed male infants had higher specific elastance, and, as result, lower variability compared to female infants. These findings support both anecdotal and known physiological differences in neonates, and quantify them for the first time.

Spontaneous breathing effort is difficult to measure and require invasive techniques, but would be extremely useful in managing ventilation. It is quantified in this research using basis functions in combination with $Edrs$ in both adults and neonates. In both cohorts, $Edrs$ was identified after initial fit using a recruitment basis function. The $Edrs$ term thus captures the un-modelled spontaneous breathing effort in a unique approach to the problem. Adult patients on spontaneous breathing NAVA ventilation showed large spontaneous breathing effort and 18 of 22 patients showed good correlation between AUCEdrs and tidal volume, and thus good correlation with electrical activity of the diaphragm, Eadi. Neonates showed six commonly occurring $Edrs$ profiles, which captured both spontaneous breathing effort and asynchronous coughs. Overall, the combined, sequential use of basis functions and $Edrs$ were able to separate modelled patient lung condition and un-modelled spontaneous breathing efforts and asynchrony. This method allows estimations of patient effort without the need of external and invasive sensors, and is a unique result in the field.

Overall, this thesis presents new models and methods and validation of existing mod-

els in identifying physiological pulmonary mechanics in both adults and neonates. The neonatal research and data are the first in-depth study on neonatal respiratory mechanics, and revealed further insight into neonatal mechanics. The model fitting on neonates also showed underlying elastance and identified and/or verified known physiologies. The research on spontaneous breathing effort was able to accurately capture patient effort and asynchrony without the need of extra invasive sensors or procedures creating a unique new model-based tool with significant clinical potential.

CHAPTER 11

Future Work

The work performed in this thesis shows good basis for future work. The models developed could be further validated and be applied in clinical settings with goal assisting MV care. The identified physiological trends can also be further improved with larger patient numbers. Several potential works that extends existing research is presented.

11.1 Larger NICU data set for validation

The NICU cohort used in this thesis was small in patient numbers (N=9), but made up a large data set in breaths(535,428 breaths). However, with larger patient numbers, more clinical outcomes can be validated. Morphine is administered to some neonates and it is known to have some sedative effect (Chase et al., 2004), given larger patient numbers and data with more detailed timings of such administration, morphine and its impact on MV can also be observed and validated. Further validation on sub-cohort studies presented in Chapter 7 can be performed. Although work performed in this thesis showed promising results which validates such physiological observation with identified elastance, with larger data set again, can be further validated.

11.2 Sex differences in adults

The sex differences in neonates showed noticeable difference in elastance for male and female infants. There are studies which looks at sex differences in neonates (Torday et al., 1981; Miller and Futrakul, 1968; Stevenson et al., 2000; Peacock et al., 2012), but there are lack of studies for it in adult MV, as adults have fully developed lungs. However, comparing elastances between male and female adults may provide further insight to lung physiology or show interesting outcomes.

11.3 Spontaneous breathing effort

Spontaneous breathing effort was quantified in both adults and neonates. The NAVA adult cohort showed good correlation between patient effort and tidal volume, which also correlate with Eadi (Moorhead et al., 2013). In neonates, the use of $Edrs$ clearly separated patient lung condition with spontaneous breathing effort and asynchrony. This method was effective at measuring patient effort in both adult and neonates and should be verified in clinical setting for further validation. It is important to understand how much the patient is breathing spontaneously, or if there is patient-ventilator asynchrony. The method defined in this thesis can perhaps be used to measure and allow clinical adjustment to reduce patient effort or allow faster transition into weaning, presenting significant opportunity for clinical impact. This tool is particularly useful as it does not require external invasive sensors or other measuring techniques.

11.4 CURE Trial

The CURE RCT should commence as soon as possible. The protocol has been finalised, ethics has been updated. Future work is required on implementation of Draeger and Hamiltion ventilation communication on CURE Soft and new mounting for hardware needs to be developed and manufactured. Once hardware and software is re-established,

software should be taught to participating clinical staffs. After the teaching, CURE trial can finally start.

APPENDIX A

Appendix

A.1 Appendix A

This appendix includes additional results from Chapter 5.

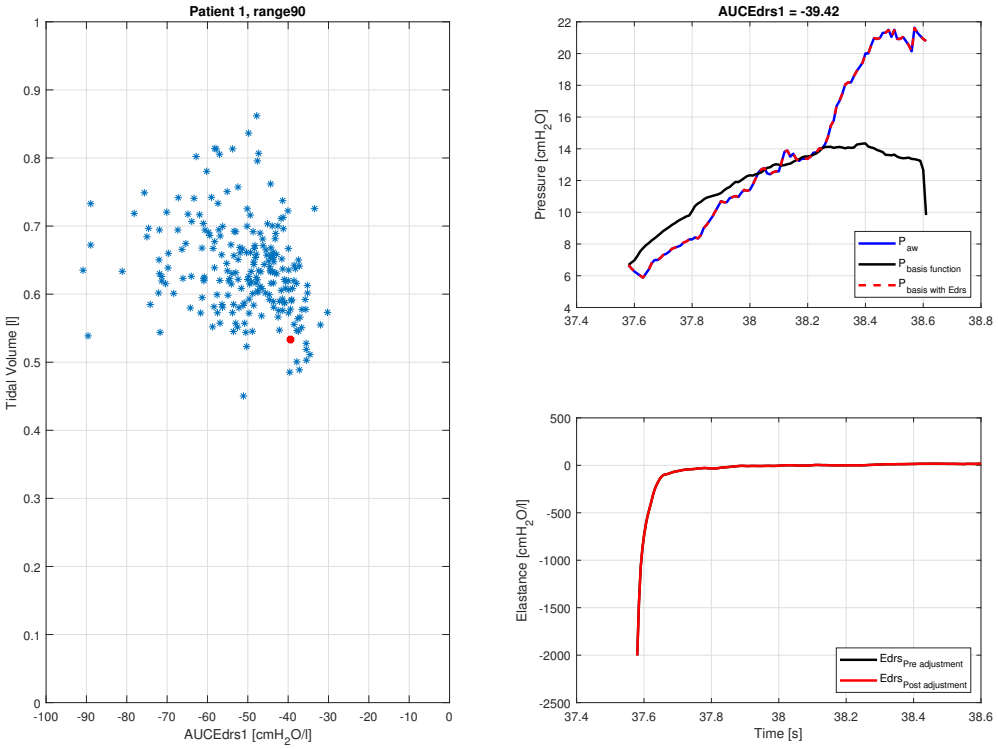

Figure A.1: Scatter plot of $AUCEdrs$ and Vt from Patient 1.

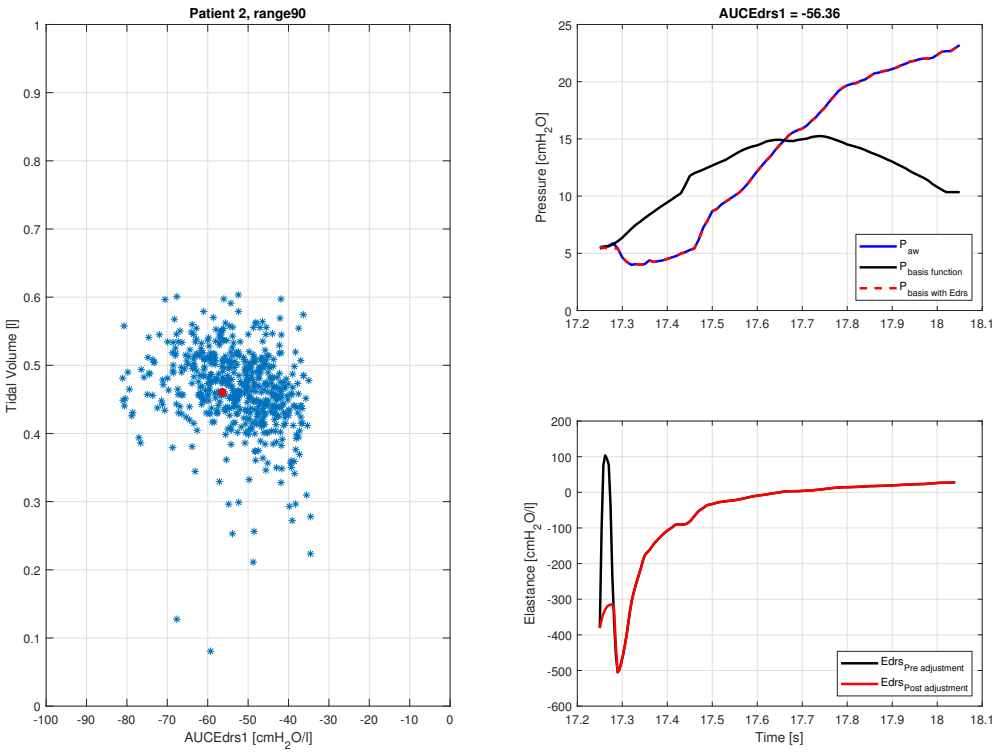

Figure A.2: Scatter plot of $AUCEdrs$ and Vt from Patient 2.

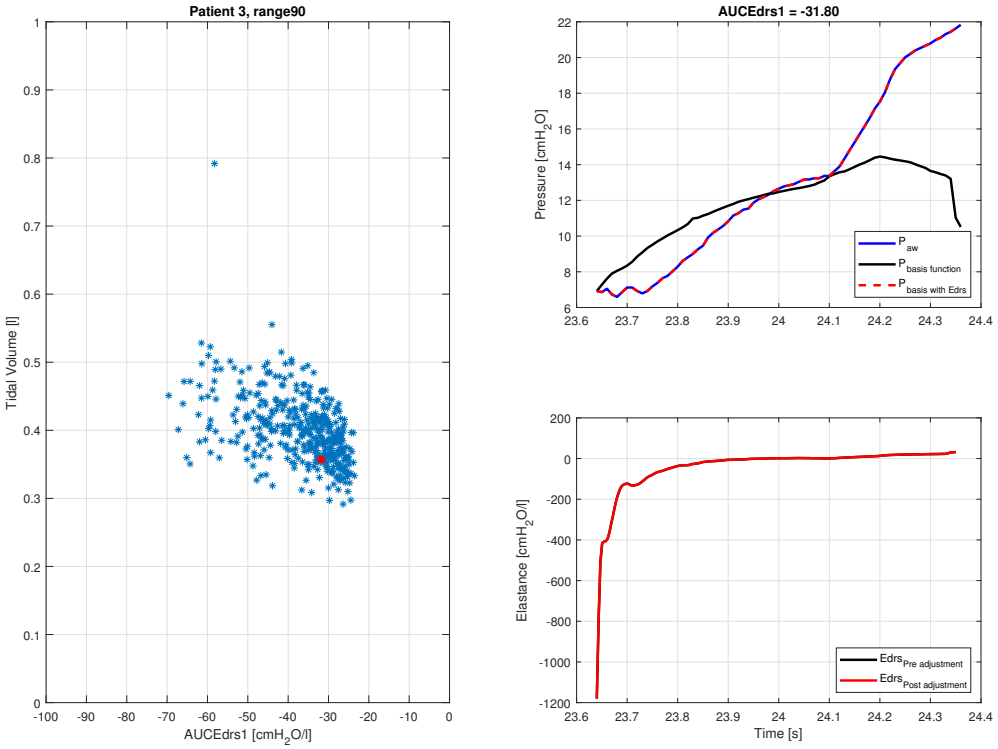

Figure A.3: Scatter plot of $AUCEdrs$ and Vt from Patient 3.

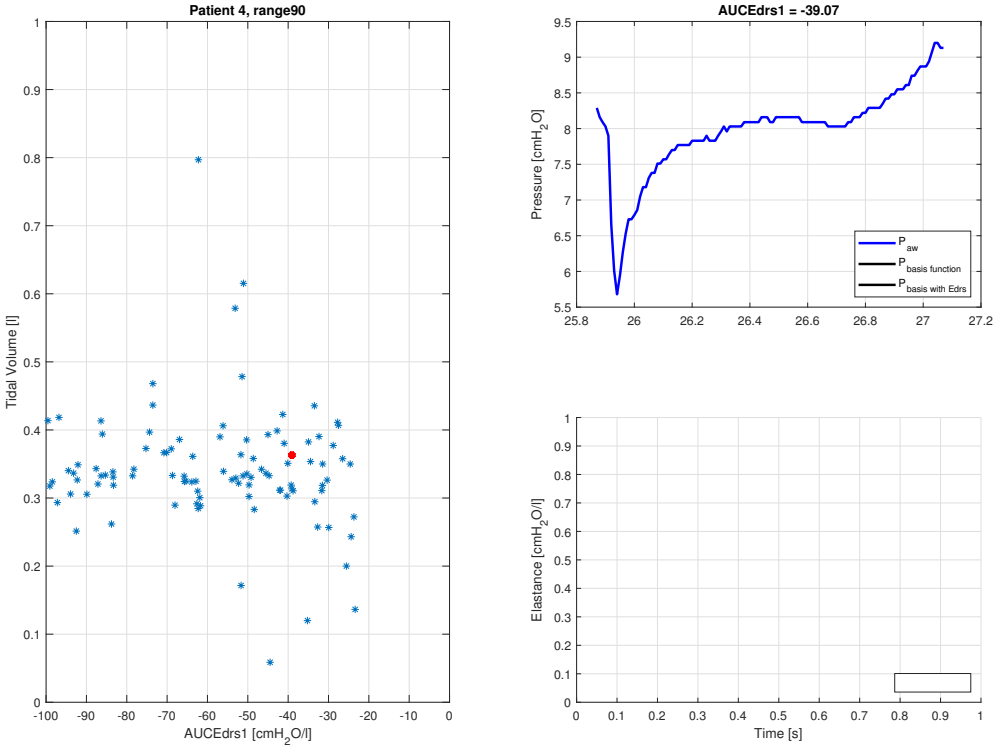

Figure A.4: Scatter plot of $AUCEdrs$ and Vt from Patient 4.

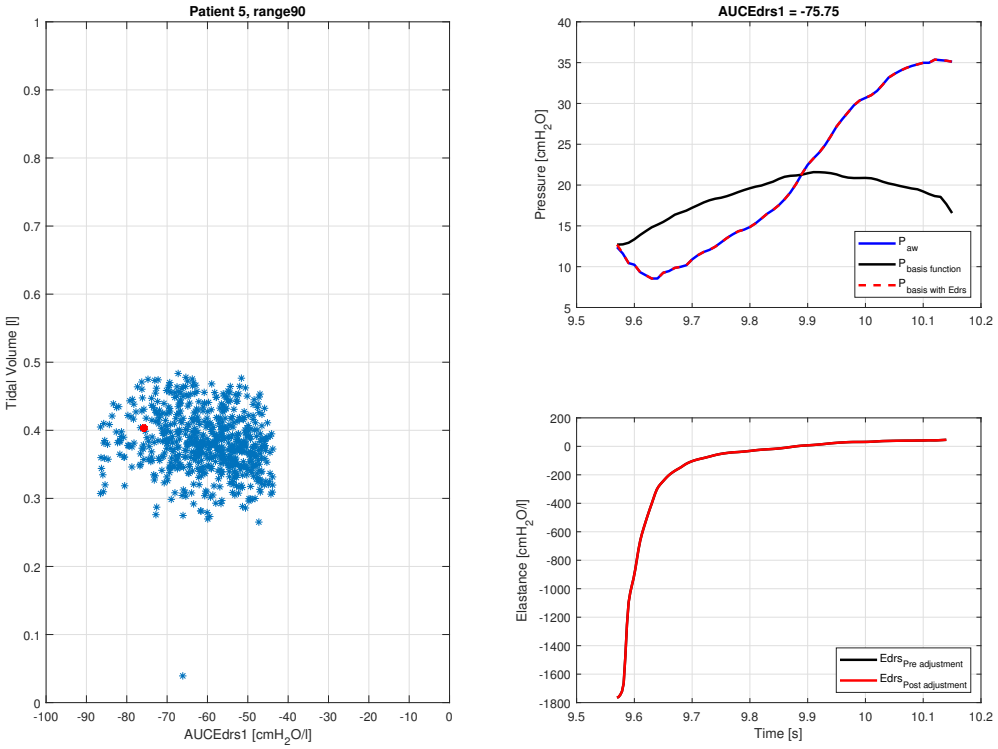

Figure A.5: Scatter plot of $AUCEdrs$ and Vt from Patient 5.

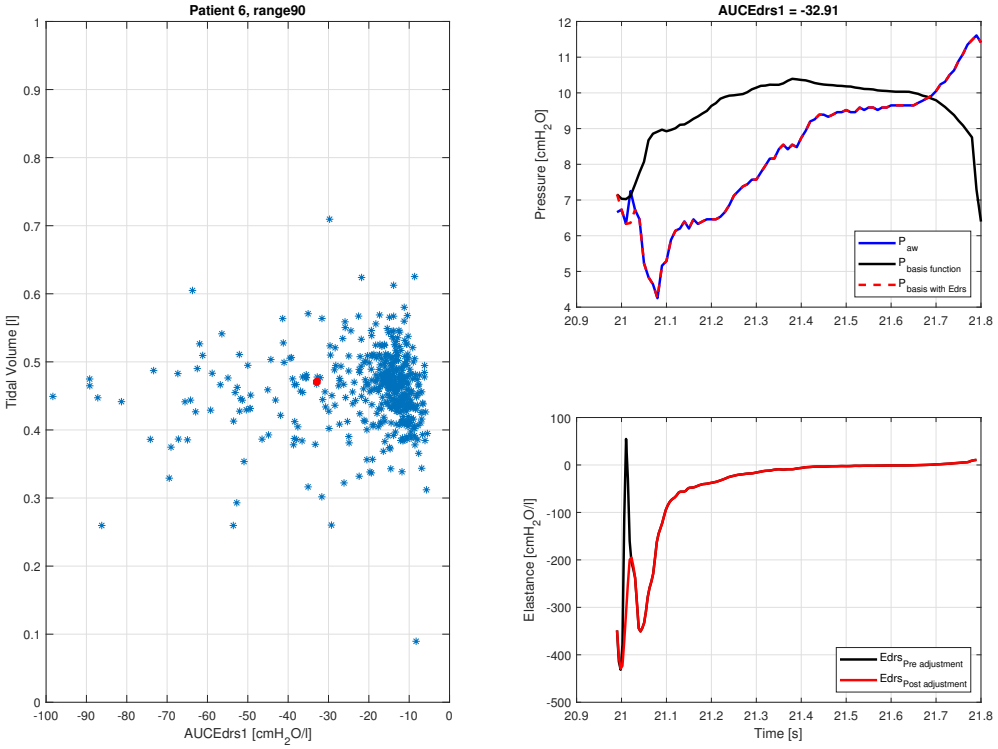

Figure A.6: Scatter plot of $AUCEdrs$ and Vt from Patient 6.

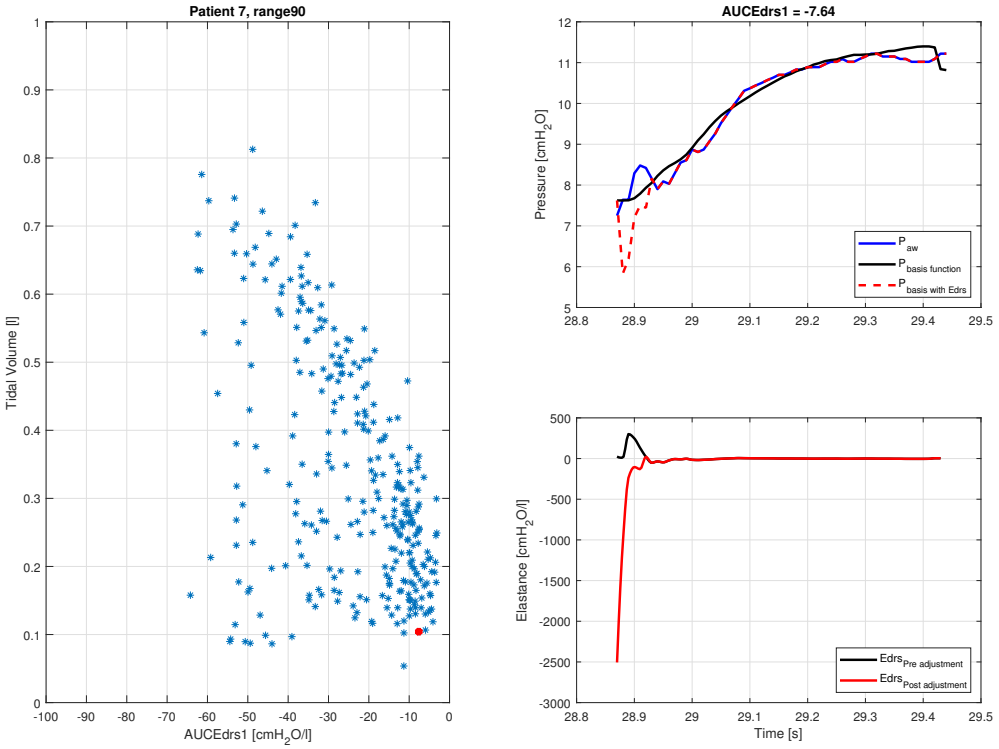

Figure A.7: Scatter plot of $AUCEdrs$ and Vt from Patient 7.

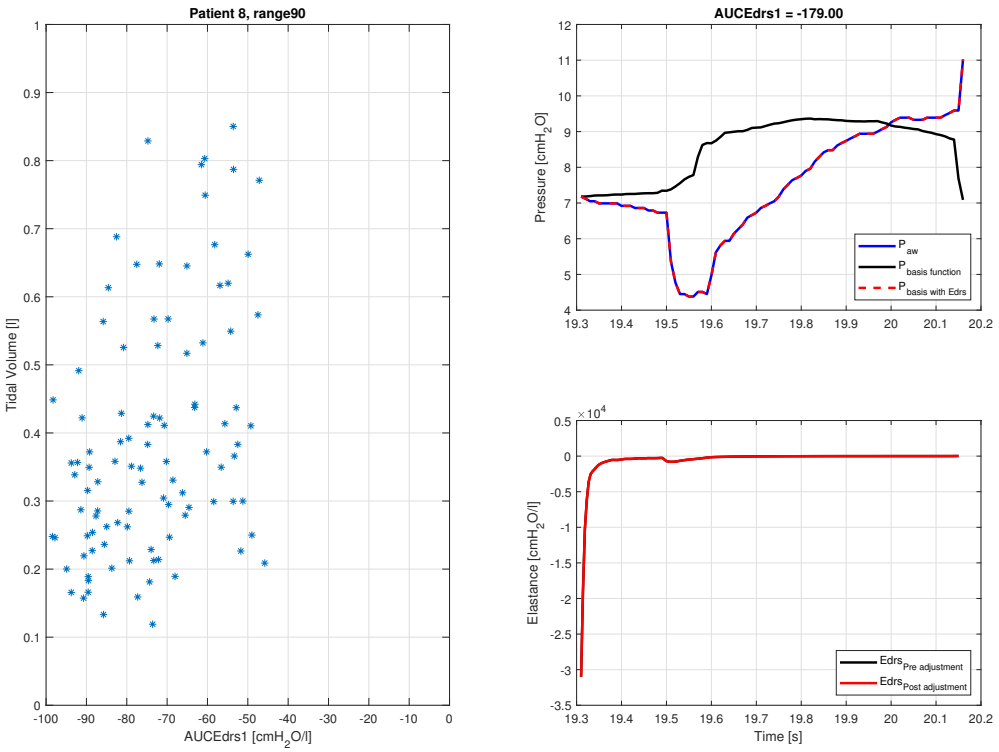

Figure A.8: Scatter plot of $AUCEdrs$ and Vt from Patient 8N.

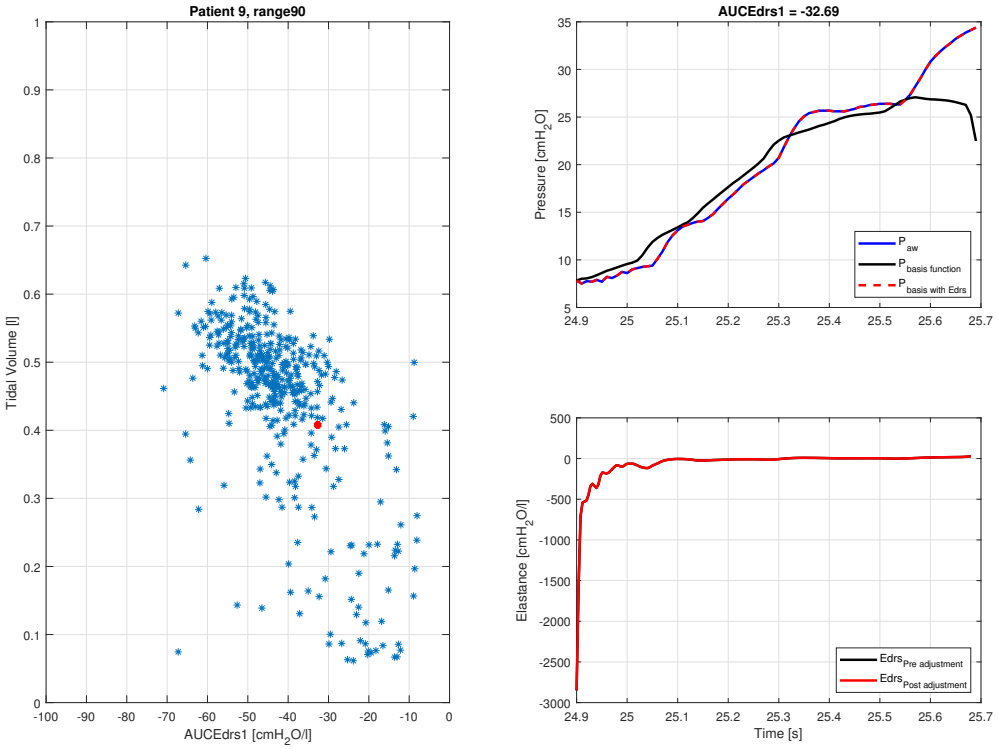

Figure A.9: Scatter plot of $AUCEdrs$ and Vt from Patient 9.

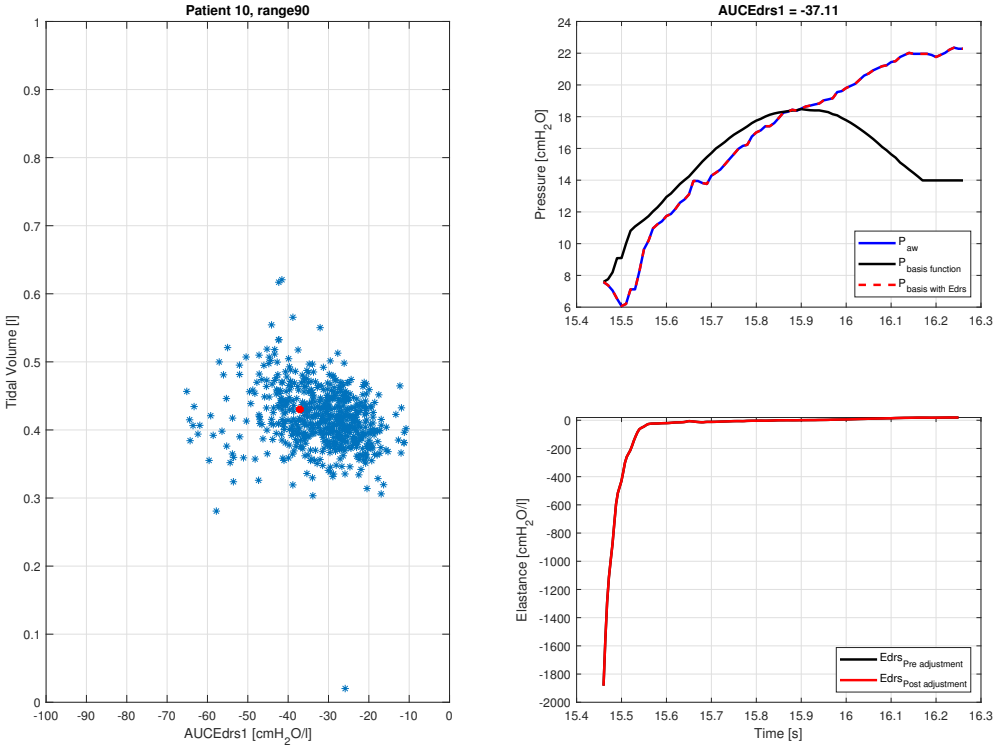

Figure A.10: Scatter plot of $AUCEdrs$ and Vt from Patient 10.

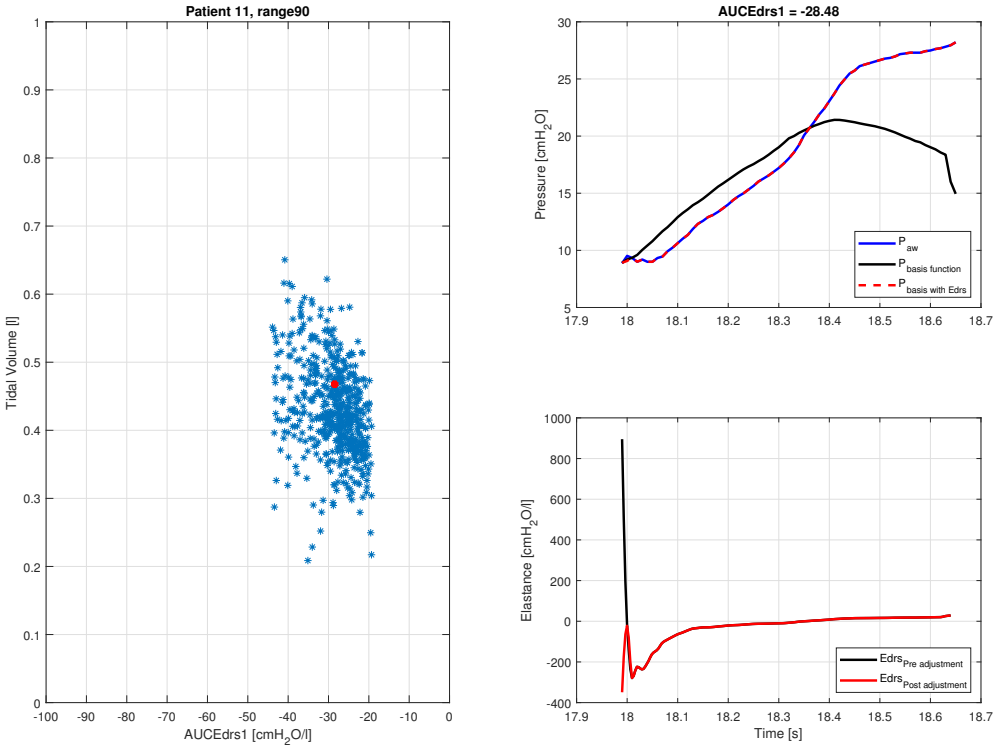

Figure A.11: Scatter plot of $AUCEdrs$ and Vt from Patient 11.

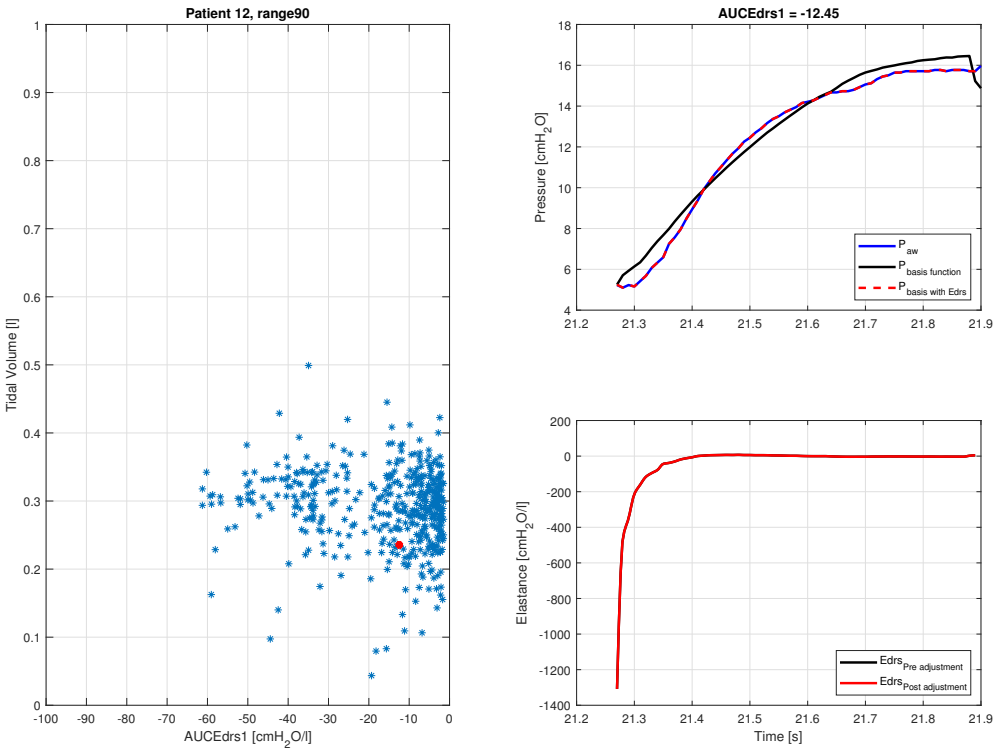

Figure A.12: Scatter plot of $AUCEdrs$ and Vt from Patient 12.

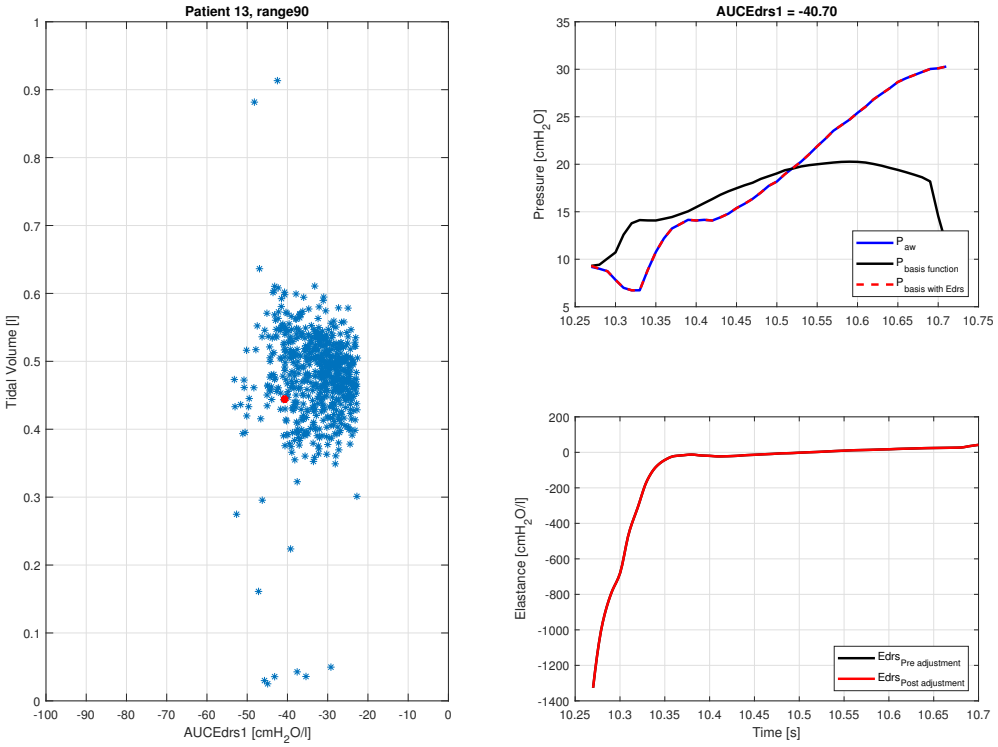

Figure A.13: Scatter plot of $AUCEdrs$ and Vt from Patient 13.

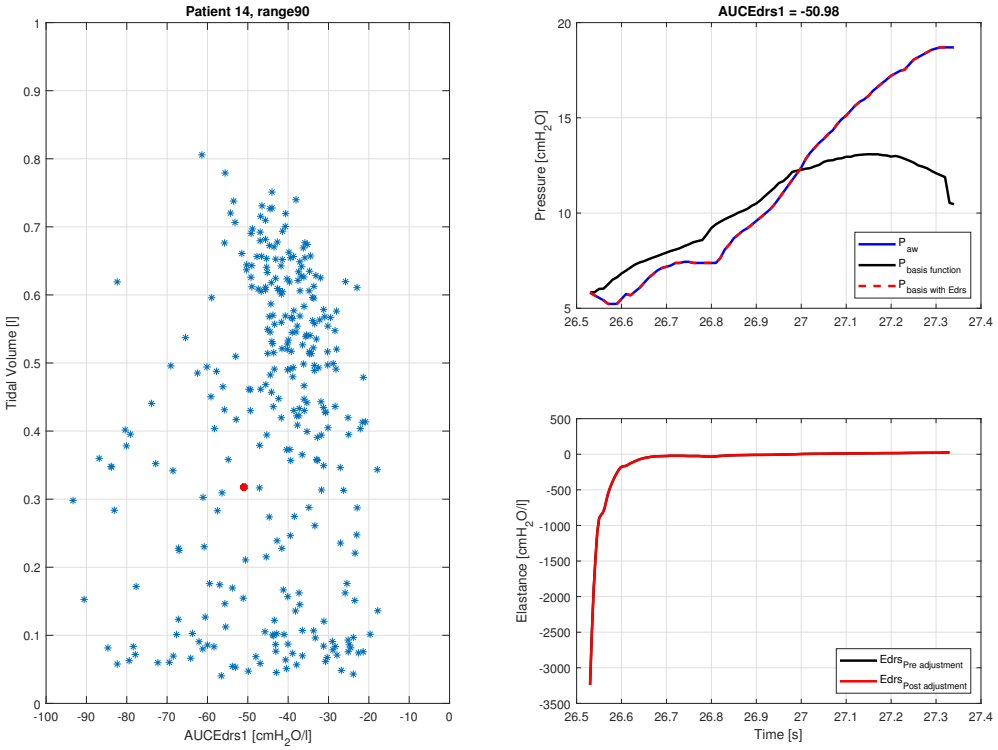

Figure A.14: Scatter plot of $AUCEdrs$ and Vt from Patient 14.

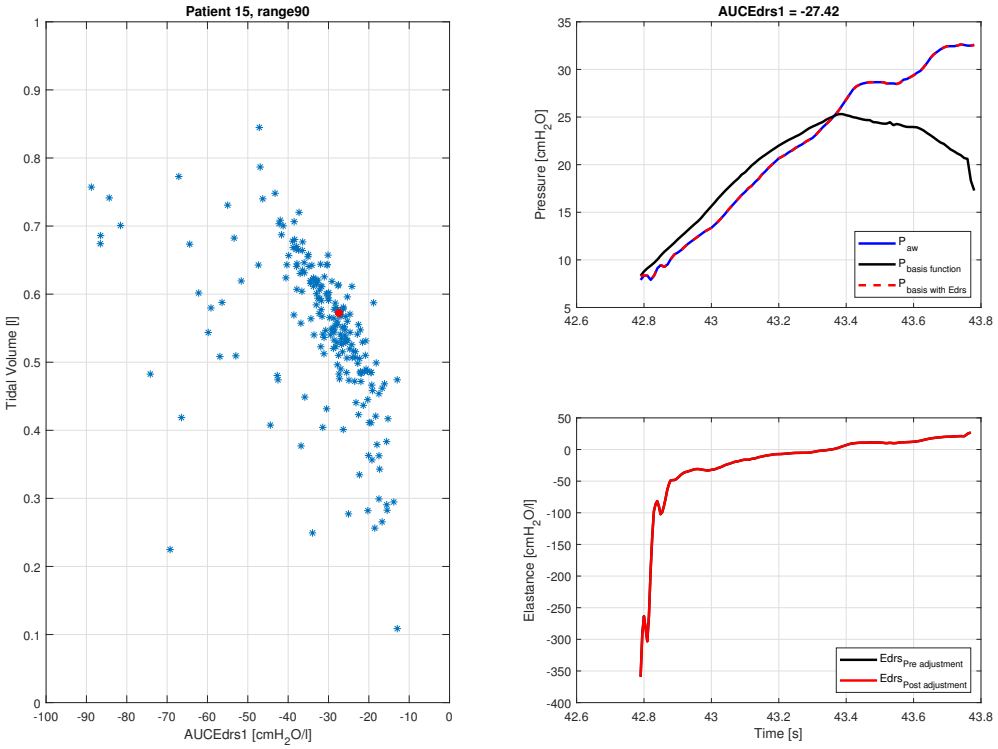

Figure A.15: Scatter plot of $AUCEdrs$ and Vt from Patient 15.

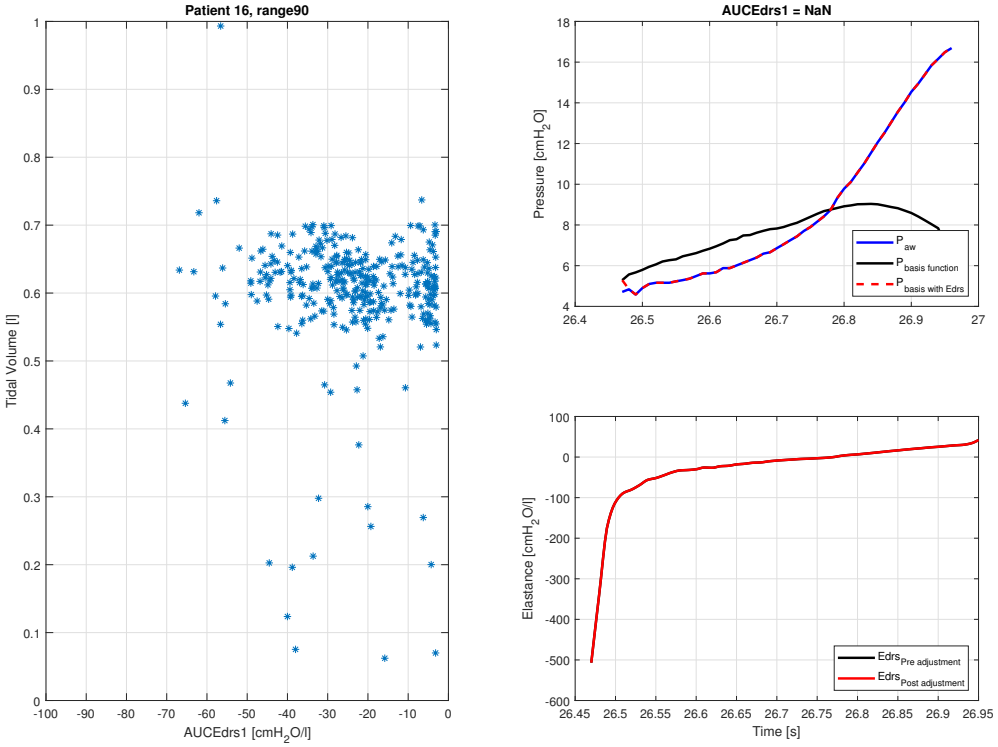

Figure A.16: Scatter plot of $AUCEdrs$ and Vt from Patient 16.

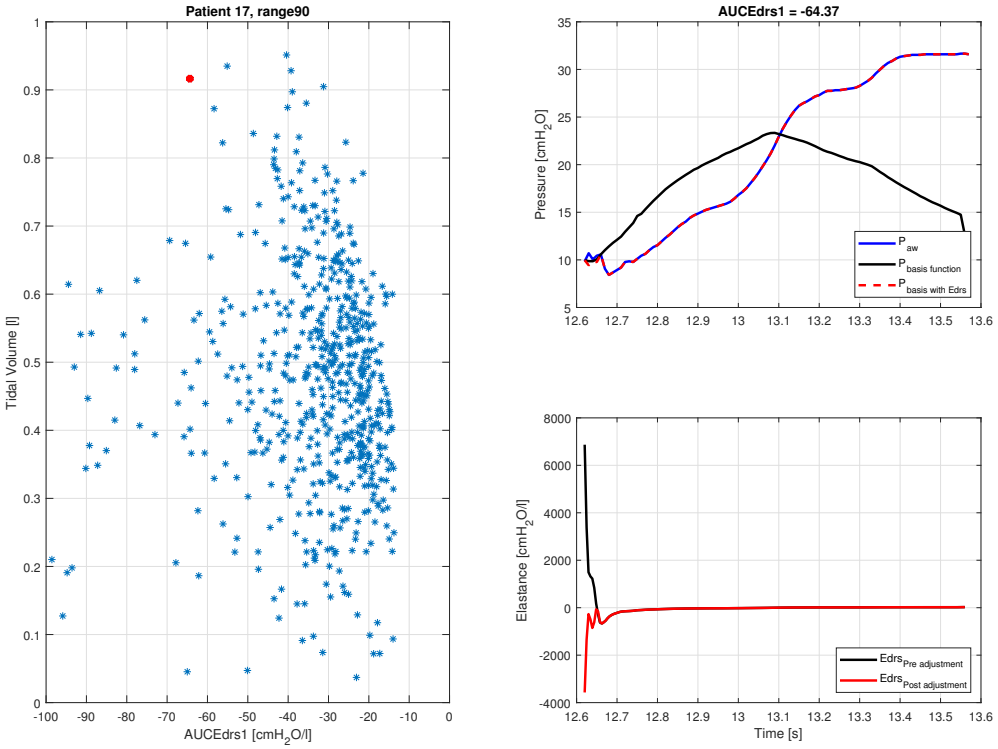

Figure A.17: Scatter plot of $AUCEdrs$ and Vt from Patient 17.

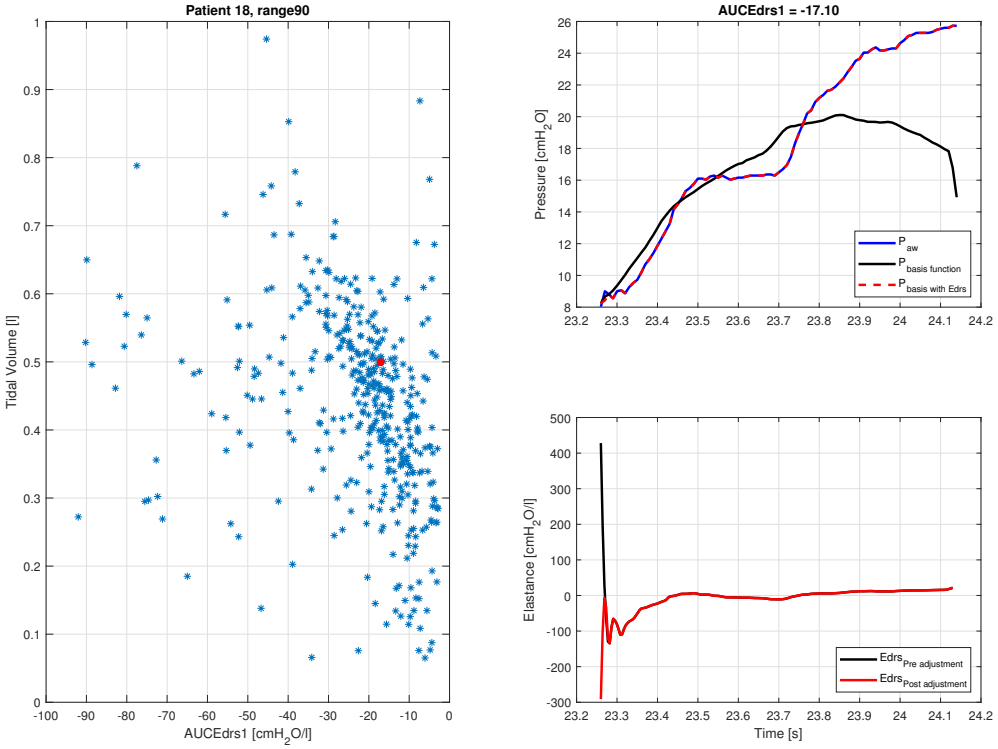

Figure A.18: Scatter plot of $AUCEdrs$ and Vt from Patient 18.

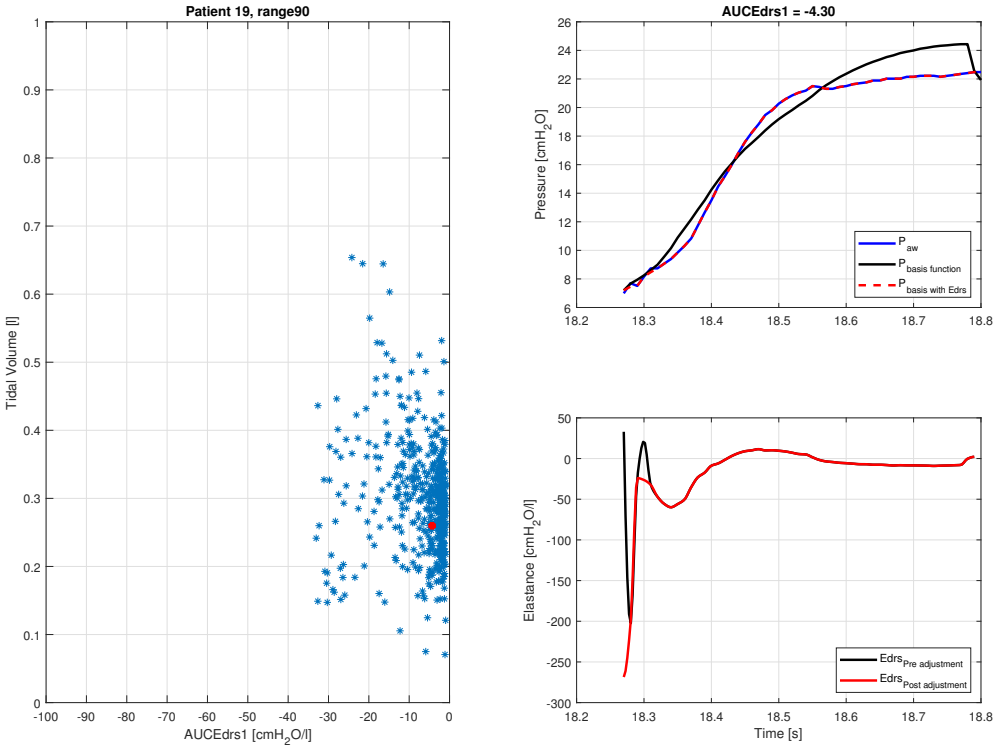

Figure A.19: Scatter plot of $AUCEdrs$ and Vt from Patient 19.

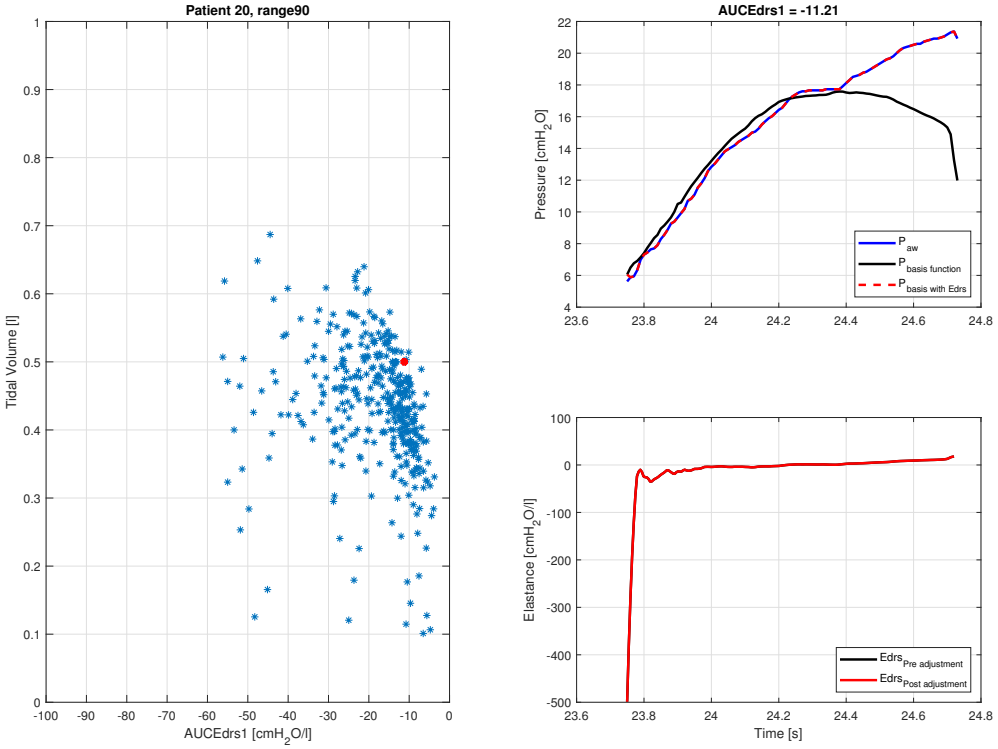

Figure A.20: Scatter plot of $AUCEdrs$ and Vt from Patient 20.

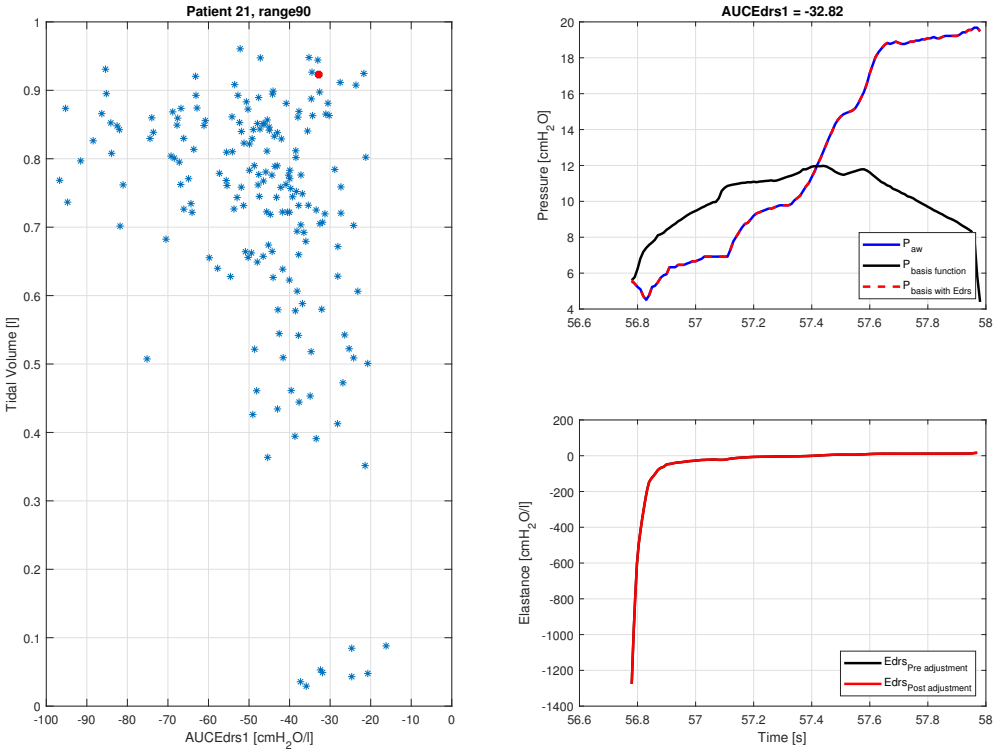

Figure A.21: Scatter plot of $AUCEdrs$ and Vt from Patient 21.

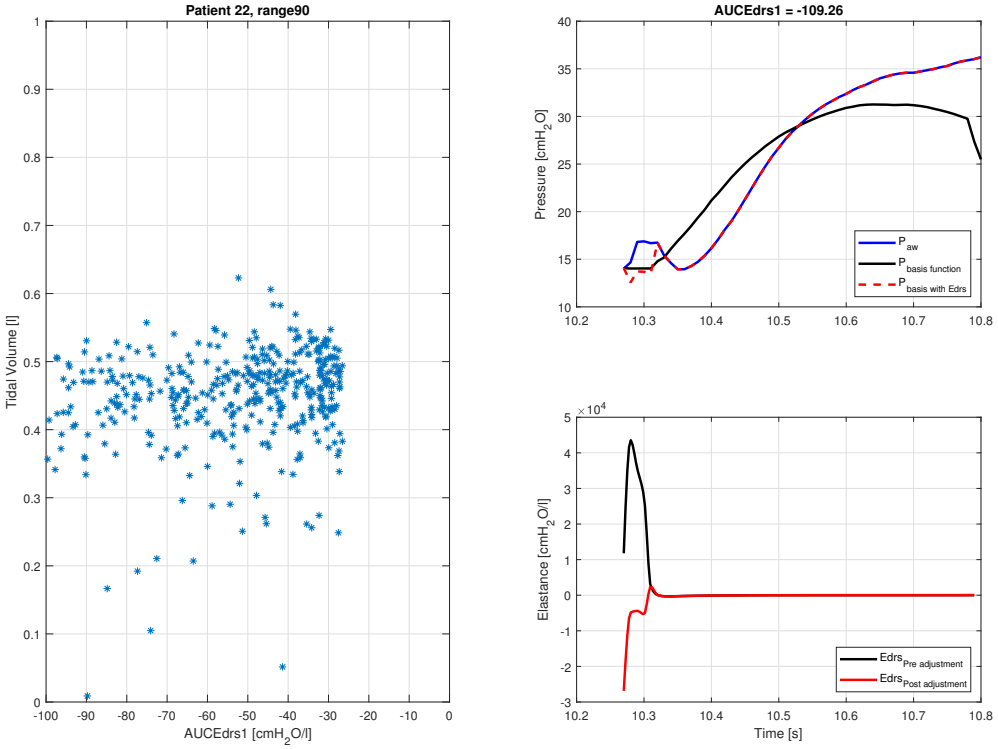

Figure A.22: Scatter plot of $AUCEdrs$ and Vt from Patient 22.

Bibliography

Akobeng, A. K. Understanding randomised controlled trials. *Archives of Disease in Childhood*, 90(8):840–844, 2005. ISSN 00039888. doi: 10.1136/adc.2004.058222.

Albaiceta, G. M. and Blanch, L. Beyond volutrauma in ARDS: The critical role of lung tissue deformation. *Critical Care*, 15(2), 2011. ISSN 13648535. doi: 10.1186/cc10052.

Altman, D. G. and Bland, J. M. Measurement in Medicine: The Analysis of Method Comparison Studies. *The Statistician*, 32(3):307, sep 1983. ISSN 00390526. doi: 10.2307/2987937. URL https://www.jstor.org/stable/2987937?origin=crossref.

Altman, D. Statistics and Ethics in Medical Research. *British Medical Journal (Clinical research ed.)*, 282(6268):990, 1981. ISSN 02670623. doi: 10.1136/bmj.282.6268.990.

Amato, M. B., Meade, M. O., Slutsky, A. S., Brochard, L., Costa, E. L., Schoenfeld, D. A., Stewart, T. E., Briel, M., Talmor, D., Mercat, A., Richard, J.-C. M., Carvalho, C. R., and Brower, R. G. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, 372(8):747–755, feb 2015. ISSN 0028-4793. doi: 10.1056/NEJMsa1410639. URL http://www.nejm.org/doi/10.1056/NEJMsa1410639.

Amato, M. B. P., Barbas, C. S. V., Medeiros, D. M., Magaldi, R. B., Schettino, G. D. P. P., Lorenzi-Filho, G., Kairalla, R. A., Deheinzelin, D., Munoz, C., Oliveira, R., Takagaki, T. Y., and Carvalho, C. R. R. Effect of a protective-ventilation strategy on mortality in

the acute respiratory distress syndrome. *New England Journal of Medicine*, 338(6): 347–354, 1998. ISSN 00284793. doi: 10.1056/NEJM199802053380602.

Amerling, R., Winchester, J. F., and Ronco, C. Guidelines have done more harm than good. *Blood Purification*, 26(1):73–76, 2008. ISSN 02535068. doi: 10.1159/000110569.

Baraldi, E. and Filippone, M. Chronic Lung Disease after Premature Birth. *New England Journal of Medicine*, 357(19):1946–1955, 2007. ISSN 0028-4793. doi: 10.1056/NEJMra067279. URL http://www.nejm.org/doi/abs/10.1056/NEJMc073362http://www.nejm.org/doi/abs/10.1056/NEJMra067279.

Bates, J. H. T. *Lung Mechanics. An Inverse Modeling Approach*. Cambridge University Press, 2009. ISBN 9780521509602.

Ben-Tal, A. Simplified models for gas exchange in the human lungs. *Journal of Theoretical Biology*, 238(2):474–495, 2006. ISSN 00225193. doi: 10.1016/j.jtbi.2005.06.005.

Bernard, G. R., Artigas, A., Brigham, K. L., Carlet, J., Falke, K., Hudson, L., Lamy, M., LeGall, J. R., Morris, A., and Spragg, R. Report of the American-European consensus conference on ARDS: Definitions, mechanisms, relevant outcomes and clinical trial coordination. *Intensive Care Medicine*, 20(3):225–232, 1994. ISSN 03424642. doi: 10.1007/BF01704707.

Bersten, A. D., Edibam, C., Hunt, T., Moran, J., and The Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and Mortality of Acute Lung Injury and the Acute Respiratory Distress Syndrome in Three Australian States. *American Journal of Respiratory Critical Care Medicine*, 165(13):443–448, 2002. ISSN 1073449X. doi: 10.1164/rccm.2101124.

Bhutani, V. K., Sivieri, E. M., Md, S. A., and Shaffer Phd, T. H. Evaluation of neonatal pulmonary mechanics and energetics: A two factor least mean square analysis. *Pediatric Pulmonology*, 4(3):150–158, 1988. ISSN 10990496. doi: 10.1002/ppul.1950040306.

Blanch, L., Sales, B., Montanya, J., Lucangelo, U., Oscar, G. E., Villagra, A., Chacon, E.,

Estruga, A., Borelli, M., Burgueño, M. J., Oliva, J. C., Fernandez, R., Villar, J., Kacmarek, R., and Murias, G. Validation of the Better Care® system to detect ineffective efforts during expiration in mechanically ventilated patients: A pilot study. *Intensive Care Medicine*, 38(5):772–780, 2012. ISSN 14321238. doi: 10.1007/s00134-012-2493-4.

Blanch, L., Villagra, A., Sales, B., Montanya, J., Lucangelo, U., Luján, M., García-Esquirol, O., Chacón, E., Estruga, A., Oliva, J. C., Hernández-Abadia, A., Albaiceta, G. M., Fernández-Mondejar, E., Fernández, R., Lopez-Aguilar, J., Villar, J., Murias, G., and Kacmarek, R. M. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Medicine*, 41(4):633–641, 2015. ISSN 14321238. doi: 10.1007/s00134-015-3692-6.

Boles, J.-M., Bion, J., Connors, A., Herridge, M., Marsh, B., Melot, C., Pearl, R., Silverman, H., Stanchina, M., Vieillard-Baron, A., and Welte, T. Weaning from mechanical ventilation. *European Respiratory Journal*, 29(5):1033–1056, may 2007. ISSN 0903-1936. doi: 10.1183/09031936.00010206. URL http://erj.ersjournals.com/cgi/doi/10.1183/09031936.00010206.

Borges, J. B., Okamoto, V. N., Matos, G. F. J., Caramez, M. P. R., Arantes, P. R., Barros, F., Souza, C. E., Victorino, J. A., Kacmarek, R. M., Barbas, C. S. V., Carvalho, C. R. R., and Amato, M. B. P. Reversibility of lung collapse and hypoxemia in early acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, 174(3):268–278, 2006. ISSN 1073449X. doi: 10.1164/rccm.200506-976OC.

Bos, L. D., Martin-Loeches, I., and Schultz, M. J. ARDS: Challenges in patient care and frontiers in research. *European Respiratory Review*, 27(147):1–9, 2018. ISSN 16000617. doi: 10.1183/16000617.0107-2017. URL http://dx.doi.org/10.1183/16000617.0107-2017.

Brander, L. and Slutsky, A. S. Assisted spontaneous breathing during early acute lung injury. *Critical care (London, England)*, 10(1):102, 2006. ISSN 1466-609X. doi: 10.

1186/cc3953. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1550866{&}tool=pmcentrez{&}rendertype=abstract.

Briel, M., Meade, M., Mercat, A., Brower, R. G., Talmor, D., Walter, S. D., Slutsky, A. S., Pullenayegum, E., Zhou, Q., Cook, D., Brochard, L., Richard, J.-C. M., Lamontagne, F., Bhatnagar, N., Stewart, T. E., and Guyatt, G. Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome. *Journal of American Medical Association*, 303(9):865–873, 2010. ISSN 0098-7484. doi: 10.1001/jama.2010.218.

Brochard, L., Roudot-Thoraval, F., Roupie, E., Delclaux, C., Chastre, J., Fernandez-Mondéjar, E., Clémenti, E., Mancebo, J., Factor, P., Matamis, D., Ranieri, M., Blanch, L., Rodi, G., Mentec, H., Dreyfuss, D., Ferrer, M., Brun-Buisson, C., Tobin, M., and Lemaire, F. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *American journal of respiratory and critical care medicine*, 158(6):1831–8, dec 1998. ISSN 1073-449X. doi: 10.1164/ajrccm.158.6.9801044. URL http://www.atsjournals.org/doi/abs/10.1164/ajrccm.158.6.9801044http://www.ncbi.nlm.nih.gov/pubmed/9847275.

Brochard, L., Martin, G. S., Blanch, L., Pelosi, P., Belda, F. J., Jubran, A., Gattinoni, L., Mancebo, J., Ranieri, V. M., Richard, J. C., Gommers, D., Vieillard-Baron, A., Pesenti, A., Jaber, S., Stenqvist, O., and Vincent, J. L. Clinical review: Respiratory monitoring in the ICU - a consensus of 16. *Crit Care*, 16(2):219, 2012. ISSN 1466-609X. doi: 10.1186/cc11146. URL http://www.ncbi.nlm.nih.gov/pubmed/22546221.

Brochard, L. Ventilation-induced lung injury exists in spontaneously breathing patients with acute respiratory failure: Yes. *Intensive Care Medicine*, 43(2):250–252, 2017. ISSN 14321238. doi: 10.1007/s00134-016-4645-4. URL http://link.springer.com/10.1007/s00134-016-4645-4.

Brochard, L., Costa, E. L. V., Schoenfeld, D. A., Ph, D., Stewart, T. E., Briel, M., Talmor,

D., Mercat, A., Richard, J.-C. M. C. M. C. M., Carvalho, C. R. R., Brower, R. G., Amato, M. B. P., Meade, M. O., Slutsky, A. S., Brochard, L., Costa, E. L. V., Schoenfeld, D. A., Stewart, T. E., Briel, M., Talmor, D., Mercat, A., Richard, J.-C. M. C. M. C. M., Carvalho, C. R. R., Brower, R. G., Ph, D., Stewart, T. E., Briel, M., Talmor, D., Mercat, A., Richard, J.-C. M. C. M. C. M., Carvalho, C. R. R., Brower, R. G., Amato, M. B. P., Meade, M. O., Slutsky, A. S., Brochard, L., Costa, E. L. V., Schoenfeld, D. A., Stewart, T. E., Briel, M., Talmor, D., Mercat, A., Richard, J.-C. M. C. M. C. M., Carvalho, C. R. R., Brower, R. G., Ph, D., Stewart, T. E., Briel, M., Talmor, D., Mercat, A., Richard, J.-C. M. C. M. C. M., Carvalho, C. R. R., and Brower, R. G. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, 372(8):747–755, feb 2015. ISSN 15334406. doi: 10.1056/NEJMsa1410639. URL http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed{&}id=25693014{&}retmode=ref{&}cmd=prlinks{%}5Cnpapers3://publication/doi/10.1056/NEJMsa1410639http://www.nejm.org/doi/10.1056/NEJMsa1410639.

Brochard, L., Slutsky, A., and Pesenti, A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *American Journal of Respiratory and Critical Care Medicine*, 195(4):438–442, 2017. ISSN 15354970. doi: 10.1164/rccm.201605-1081CP.

Brower, R. G., Ware, L. B., Berthiaume, Y., and Matthay, M. A. Treatment of ARDS. *Chest*, 120(4):1347–1367, 2001. ISSN 00123692. doi: 10.1378/chest.120.4.1347.

Brower, R. G., Lanken, P. N., MacIntyre, N., Matthay, M. A., Morris, A., Ancukiewicz, M., Schoenfeld, D., and Thompson, B. T. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *New England Journal of Medicine*, 351(4):327–336+411, jul 2004. ISSN 00284793. doi: 10.1056/NEJMoa032193. URL http://www.nejm.org/doi/abs/10.1056/NEJMoa032193.

Brower, R. G. E. A., England, T. N., Acute, T., Distress, R., Network, S., England, T. N., Brower, R. G. E. A., Matthay, M. A., Morris, A., Schoenfeld, D., Thompson, B. T., Wheeler, A., Acute Respiratory Distress Syndrome Network, Brower, R. G. E. A.,

Matthay, M. A., Morris, A., Schoenfeld, D., Thompson, B. T., Wheeler, A., and ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *The New England journal of medicine*, 342(18):1301–1308, 2000. ISSN 0028-4793. doi: 10.1056/NEJM200005043421801. URL http://www.ncbi.nlm.nih.gov/pubmed/10793162.

Brown, M. K. and DiBlasi, R. M. Mechanical Ventilation of the Premature Neonate. *Respiratory Care*, 56(9):1298–1313, sep 2011. ISSN 0020-1324. doi: 10.4187/respcare.01429. URL http://www.ncbi.nlm.nih.gov/pubmed/6894519http://rc.rcjournal.com/cgi/doi/10.4187/respcare.01429.

Burchardi, H. Aims of Sedation / Analgesia. *Minerva Anestesiologica*, 70:137–143, 2004.

Calvert, M., Kyte, D., Mercieca-Bebber, R., Slade, A., Chan, A. W., and King, M. T. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols the spirit-pro extension. *JAMA - Journal of the American Medical Association*, 319(5):483–494, 2018. ISSN 15383598. doi: 10.1001/jama.2017.21903.

Carey, M. A., Card, J. W., Voltz, J. W., Arbes, S. J., Germolec, D. R., Korach, K. S., and Zeldin, D. C. It's all about sex: gender, lung development and lung disease. *Trends in Endocrinology and Metabolism*, 18(8):308–313, 2007. ISSN 10432760. doi: 10.1016/j.tem.2007.08.003.

Carlucci, A., Pisani, L., Ceriana, P., Malovini, A., and Nava, S. Patient-ventilator asynchronies: may the respiratory mechanics play a role? *Critical care (London, England)*, 17(2):R54, 2013. ISSN 1466-609X. doi: 10.1186/cc12580. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3672543{&}tool=pmcentrez{&}rendertype=abstract.

Carroll, J. L. and Agarwal, A. Development of ventilatory control in infants. *Paediatric Respiratory Reviews*, 11(4):199–207, 2010. ISSN 15260542. doi: 10.1016/j.prrv.2010.06.002. URL http://dx.doi.org/10.1016/j.prrv.2010.06.002.

Carvalho, A., Jandre, F. C., Pino, A. V., Bozza, F. A., Salluh, J., Rodrigues, R., Ascoli, F. O., and Giannella-Neto, A. Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. *Critical Care*, 11(4):R86, 2007. ISSN 13648535. doi: 10.1186/cc6093. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2206498{&}tool=pmcentrez{&}rendertype=abstract.

Carvalho, A. R., Bergamini, B. C., Carvalho, N. S., Cagido, V. R., Neto, A. C., Jandre, F. C., Zin, W. A., and Giannella-Neto, A. Volume-independent elastance: A useful parameter for open-lung positive end-expiratory pressure adjustment. *Anesthesia and Analgesia*, 116(3):627–633, 2013a. ISSN 00032999. doi: 10.1213/ANE.0b013e31824a95ca.

Carvalho, C. G., Silveira, R. C., and Procianoy, R. S. Ventilator-induced lung injury in preterm infants. *Revista Brasileira de Terapia Intensiva*, 25(4):319–326, 2013b. ISSN 0103-507X. doi: 10.5935/0103-507X.20130054. URL http://www.gnresearch.org/doi/10.5935/0103-507X.20130054.

Cavalcanti, A. B. and ART Investigators. Effect of lung recruitment and titrated Positive End-Expiratory Pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome - A randomized clinical trial. *JAMA - Journal of the American Medical Association*, 318(14):1335–1345, 2017. ISSN 15383598. doi: 10.1001/jama.2017.14171.

Chakson, J., McNearney, E. J., Argus, F., Sutherland, C. J., Dickson, J., Redmond, D., Kim, K. T., and Chase, J. G. Analysis of Neonatal Pulmonary Mechanics. *IFAC-PapersOnLine*, 50(1):6654–6659, 2017. ISSN 24058963. doi: 10.1016/j.ifacol.2017.08.1532. URL https://doi.org/10.1016/j.ifacol.2017.08.1532.

Chao, D. C., Scheinhorn, D. J., and Stearn-Hassenpflug, M. Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. *Chest*, 112(6):1592–1599, 1997. ISSN 00123692. doi: 10.1378/chest.112.6.1592.

Chase, J. G., Compte, A. J. L., Preiser, J.-c., Shaw, G. M., Penning, S., Desaive, T., Le

Compte, A. J., Preiser, J.-c., Shaw, G. M., Penning, S., and Desaive, T. Physiological modeling, tight glycemic control, and the ICU clinician: what are models and how can they affect practice? *Annals of intensive care*, 1(1):11, 2011. ISSN 2110-5820. doi: 10.1186/2110-5820-1-11. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3224460{&}tool=pmcentrez{&}rendertype=abstract{%}5Cnhttp://www.annalsofintensivecare.com/content/1/1/11.

Chase, J. G., Preiser, J. C., Dickson, J. L., Pironet, A., Chiew, Y. S., Pretty, C. G., Shaw, G. M., Benyo, B., Moeller, K., Safaei, S., Tawhai, M., Hunter, P., and Desaive, T. Next-generation, personalised, model-based critical care medicine: A state-of-the art review of in silico virtual patient models, methods, and cohorts, and how to validation them. *BioMedical Engineering Online*, 17(1):1–29, 2018. ISSN 1475925X. doi: 10.1186/s12938-018-0455-y. URL https://doi.org/10.1186/s12938-018-0455-y.

Chase, J., Desaive, T., and Preiser, J.-C. Virtual patients and virtual cohorts: a new way to think about the design and implementation of personalized icu treatments. In *Annual Update in Intensive Care and Emergency Medicine 2016*, pages 435–448. Springer, 2016.

Chase, J., Rudge, A. D., Shaw, G. M., Wake, G. C., Lee, D., Hudson, I. L., and Johnston, L. Modeling and control of the agitation–sedation cycle for critical care patients. *Medical Engineering & Physics*, 26(6):459–471, jul 2004. ISSN 13504533. doi: 10.1016/j.medengphy.2004.02.001. URL https://linkinghub.elsevier.com/retrieve/pii/S1350453304000268.

Chiew, Y. S., Chase, J. G., Lambermont, B., Janssen, N., Schranz, C., Moeller, K., Shaw, G. M., and Desaive, T. Physiological relevance and performance of a minimal lung model - an experimental study in healthy and acute respiratory distress syndrome model piglets. *BMC Pulmonary Medicine*, 2012. ISSN 14712466. doi: 10.1186/1471-2466-12-59.

Chiew, Y. S., Chase, J. G., Shaw, G. M., Sundaresan, A., and Desaive, T. Model-based PEEP optimisation in mechanical ventilation. *BioMedical Engineering OnLine*, 10

(1):111, 2011. ISSN 1475-925X. doi: 10.1186/1475-925X-10-111. URL http://www.biomedical-engineering-online.com/content/10/1/111.

Chiew, Y. S., Chase, J. G., Lambermont, B., Roeseler, J., Pretty, C., Bialais, E., Sottiaux, T., and Desaive, T. Effects of Neurally Adjusted Ventilatory Assist (NAVA) levels in non-invasive ventilated patients: titrating NAVA levels with electric diaphragmatic activity and tidal volume matching. *Biomedical engineering online*, 12(1):61, 2013. ISSN 1475-925X. doi: 10.1186/1475-925X-12-61. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3707774{&}tool=pmcentrez{&}rendertype=abstract.

Chiew, Y. S., Pretty, C., Docherty, P., Lambermont, B., Shaw, G. M., Desaive, T., and Chase, J. G. Time-varying respiratory system elastance: A physiological model for patients who are spontaneously breathing. *PLoS ONE*, 10(1):1–13, 2015a. ISSN 19326203. doi: 10.1371/journal.pone.0114847. URL http://dx.doi.org/10.1371/journal.pone.0114847.

Chiew, Y. S., Pretty, C. G., Beatson, A., Glassenbury, D., Major, V., Corbett, S., Redmond, D., Szlavecz, A., Shaw, G. M., and Chase, J. G. Automated logging of inspiratory and expiratory non-synchronized breathing (ALIEN) for mechanical ventilation. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS*, 2015-Novem:5315–5318, 2015b. ISSN 1557170X. doi: 10.1109/EMBC.2015.7319591.

Chiew, Y. S. W., Pretty, C. G., Shaw, G. M., Chiew, Y. S. W., Lambermont, B., Desaive, T., and Chase, J. G. Feasibility of titrating PEEP to minimum elastance for mechanically ventilated patients. *Pilot and Feasibility Studies*, 1:1–10, 2015c. ISSN 2055-5784. doi: 10.1186/s40814-015-0006-2.

Chiew, Y. S. W., Tan, C. P., Chase, J. G., Chiew, Y. S. W., Desaive, T., Ralib, A. M., and Mat Nor, M. B. Assessing mechanical ventilation asynchrony through iterative airway pressure reconstruction. *Computer Methods and Programs in Biomedicine*, 157:217–224, 2018.

ISSN 18727565. doi: 10.1016/j.cmpb.2018.02.007. URL https://doi.org/10.1016/j.cmpb.2018.02.007.

Chow, L. C., Vanderhal, A., Raber, J., and Sola, A. Are tidal volume measurements in neonatal pressure-controlled ventilation accurate? *Pediatric Pulmonology*, 34(3):196–202, sep 2002. ISSN 8755-6863. doi: 10.1002/ppul.10150. URL http://doi.wiley.com/10.1002/ppul.10150.

Clark, R. H., Slutsky, A. S., and Gerstmann, D. R. Lung Protective Strategies of Ventilation in the Neonate: What Are They? *Pediatrics*, 105(1):112–114, 2000. ISSN 0031-4005. doi: 10.1542/peds.105.1.112. URL http://pediatrics.aappublications.org/lookup/doi/10.1542/peds.105.1.112.

Colin, A. A., McEvoy, C., and Castile, R. G. Respiratory Morbidity and Lung Function in Preterm Infants of 32 to 36 Weeks' Gestational Age. *PEDIATRICS*, 126(1):115–128, jul 2010. ISSN 0031-4005. doi: 10.1542/peds.2009-1381. URL http://pediatrics.aappublications.org/cgi/doi/10.1542/peds.2009-1381.

Cools, F., Askie, L. M., Offringa, M., Asselin, J. M., Calvert, S. A., Courtney, S. E., Dani, C., Durand, D. J., Gerstmann, D. R., Henderson-Smart, D. J., Marlow, N., Peacock, J. L., Pillow, J. J., Soll, R. F., Thome, U. H., Truffert, P., Schreiber, M. D., Van Reempts, P., Vendettuoli, V., and Vento, G. Elective high-frequency oscillatory versus conventional ventilation in preterm infants: a systematic review and meta-analysis of individual patients' data. *The Lancet*, 375(9731):2082–2091, 2010. ISSN 01406736. doi: 10.1016/S0140-6736(10)60278-4.

Copland, I. and Post, M. Lung development and fetal lung growth. *Paediatric Respiratory Reviews*, 5(SUPPL. A), 2004. ISSN 15260542. doi: 10.1016/S1526-0542(04)90049-8.

Courtney, S. E., Durand, D. J., Asselin, J. M., Hudak, M. L., Aschner, J. L., and Shoemaker, C. T. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *New England Journal of Medicine*, 347(9):643–652, 2002. ISSN 0028-4793. doi: 10.1056/NEJMoa012750.

Cullen, D. J. and Caldera, D. L. The incidence of ventilator-induced pulmonary barotrauma in critically ill patients. *Anesthesiology*, 50(3):185–90, mar 1979. ISSN 0003-3022. doi: 10.1097/00000542-197903000-00003. URL http://www.ncbi.nlm.nih.gov/pubmed/373507.

Damanhuri, N. S., Docherty, P. D., Chiew, Y. S., Van Drunen, E. J., Desaive, T., and Chase, J. G. A patient-specific airway branching model for mechanically ventilated patients. *Computational and Mathematical Methods in Medicine*, 2014, 2014. ISSN 17486718. doi: 10.1155/2014/645732.

Damanhuri, N. S., Chiew, Y. S., Othman, N. A., Docherty, P. D., Pretty, C. G., Shaw, G. M., Desaive, T., and Chase, J. G. Assessing respiratory mechanics using pressure reconstruction method in mechanically ventilated spontaneous breathing patient. *Computer Methods and Programs in Biomedicine*, 130:175–185, 2016. ISSN 18727565. doi: 10.1016/j.cmpb.2016.03.025. URL http://dx.doi.org/10.1016/j.cmpb.2016.03.025.

Damanhuri, N. S., Noor Ariffin, N. N., Azlan Othman, N., Shiong Chiew, Y., Md Ralib, A., Mat Noor, M. B., D. Docherty, P., and Geoffrey Chase, J. Assessing SB effort via a non-invasive model-based method in mechanically ventilated patients in Malaysian ICU hospital. *Indonesian Journal of Electrical Engineering and Computer Science*, 15 (3):1232, sep 2019. ISSN 2502-4760. doi: 10.11591/ijeecs.v15.i3.pp1232-1240. URL http://ijeecs.iaescore.com/index.php/IJEECS/article/view/19392.

Dasta, J. F., McLaughlin, T. P., Mody, S. H., and Tak Piech, C. Daily cost of an intensive care unit day: The contribution of mechanical ventilation*. *Critical Care Medicine*, 33 (6):1266–1271, 2005. ISSN 0090-3493. doi: 10.1097/01.CCM.0000164543.14619.00.

de Matos, G. F. J., Stanzani, F., Passos, R. H., Fontana, M. F., Albaladejo, R., Caserta, R. E., Santos, D. C. B., Borges, J. B., Amato, M. B. P., and Barbas, C. S. V. How large is the lung recruitability in early acute respiratory distress syndrome: a prospective case series of patients monitored by computed tomography. *Critical care (London, England)*, 16(1):R4, 2012. ISSN 1466-609X. doi: 10.

1186/cc10602. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3396229{&}tool=pmcentrez{&}rendertype=abstract.

de Wit, M., Pedram, S., Best, A. M., and Epstein, S. K. Observational study of patient-ventilator asynchrony and relationship to sedation level. *Journal of Critical Care*, 24 (1):74–80, 2009. ISSN 08839441. doi: 10.1016/j.jcrc.2008.08.011. URL http://dx.doi.org/10.1016/j.jcrc.2008.08.011.

Definition, T. B., The ARDS Definition Task Force, and Definition, T. B. Acute Respiratory Distress Syndrome. *JAMA*, 307(23), jun 2012. ISSN 0098-7484. doi: 10.1001/jama.2012.5669. URL http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2012.5669.

Deulofeut, R., Golde, D., and Augusto, S. Treatment-by-gender effect when aiming to avoid hyperoxia in preterm infants in the NICU. *Acta Paediatrica, International Journal of Paediatrics*, 96(7):990–994, 2007. ISSN 08035253. doi: 10.1111/j.1651-2227.2007.00365.x.

Docherty, P. D., Chase, J. G., Lotz, T. F., and Desaive, T. A graphical method for practical and informative identifiability analyses of physiological models: A case study of insulin kinetics and sensitivity. *Biomedical engineering online*, 10(1):39, 2011. ISSN 1475-925X. doi: 10.1186/1475-925X-10-39. URL http://www.ncbi.nlm.nih.gov/pubmed/21615928{%}5Cnhttp://www.biomedical-engineering-online.com/content/pdf/1475-925X-10-39.pdfhttp://biomedical-engineering-online.biomedcentral.com/articles/10.1186/1475-925X-10-39.

Docherty, P. D., Schranz, C., Chiew, Y.-S., Möller, K., and Chase, J. G. Reformulation of the pressure-dependent recruitment model (prm) of respiratory mechanics. *Biomedical Signal Processing and Control*, 12:47–53, 2014.

Donn, S. M. and Boon, W. Mechanical ventilation of the neonate: Should we target volume or pressure? In *Respiratory Care*, 2009.

Dreyfuss, D. and Saumon, G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive Care Medicine*, 18(3):139–141, 1992. ISSN 14321238. doi: 10.1007/BF01709236.

Dreyfuss, D. and Saumon, G. Ventilator-induced lung injury: lessons from experimental studies. *American journal of respiratory and critical care medicine*, 157(1):294–323, jan 1998. ISSN 1073-449X. doi: 10.1164/ajrccm.157.1.9604014. URL http://www.ncbi.nlm.nih.gov/pubmed/9445314.

Ducharme-Crevier, L., Beck, J., Essouri, S., Jouvet, P., and Emeriaud, G. Neurally adjusted ventilatory assist (NAVA) allows patient-ventilator synchrony during pediatric noninvasive ventilation: a crossover physiological study. *Critical care (London, England)*, 19(1):44, 2015. ISSN 1466-609X. doi: 10.1186/s13054-015-0770-7. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4342194{&}tool=pmcentrez{&}rendertype=abstract.

Dunkel, B. Acute Lung Injury and Acute Respiratory Distress Syndrome in Foals. *Clinical Techniques in Equine Practice*, 5(2):127–133, 2006. ISSN 15347516. doi: 10.1053/j.ctep.2006.03.006.

Epstein, S. K. How often does patient-ventilator asynchrony occur and what are the consequences? *Respiratory Care*, 56(1):25–35, 2011. ISSN 00201324. doi: 10.4187/respcare.01009.

Estenssoro, E., Dubin, A., Laffaire, E., Canales, H. S., Saenz, G., Moseinco, M., and Bachetti, P. Impact of positive end-expiratory pressure on the definition of acute respiratory distress syndrome. *Intensive Care Medicine*, 29(11):1936–1942, nov 2003. ISSN 0342-4642. doi: 10.1007/s00134-003-1943-4. URL http://link.springer.com/10.1007/s00134-003-1943-4.

Fan, E., Wilcox, M. E., Brower, R. G., Stewart, T. E., Mehta, S., Lapinsky, S. E., Meade, M. O., and Ferguson, N. D. Recruitment Maneuvers for Acute Lung Injury. *American Journal of Respiratory and Critical Care Medicine*, 178(11):1156–1163, 2008. ISSN 1073-

449X. doi: 10.1164/rccm.200802-335OC. URL http://www.atsjournals.org/doi/abs/10.1164/rccm.200802-335OC.

Fan, E., Del Sorbo, L., Goligher, E. C., Hodgson, C. L., Munshi, L., Walkey, A. J., Adhikari, N. K., Amato, M. B., Branson, R., Brower, R. G., Ferguson, N. D., Gajic, O., Gattinoni, L., Hess, D., Mancebo, J., Meade, M. O., McAuley, D. F., Pesenti, A., Ranieri, V. M., Rubenfeld, G. D., Rubin, E., Seckel, M., Slutsky, A. S., Talmor, D., Thompson, B. T., Wunsch, H., Uleryk, E., Brozek, J., and Brochard, L. J. An official American Thoracic Society/European Society of intensive care medicine/society of critical care medicine clinical practice guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. *American Journal of Respiratory and Critical Care Medicine*, 195(9):1253–1263, 2017. ISSN 15354970. doi: 10.1164/rccm.201703-0548ST.

Fan, E., Brodie, D., and Slutsky, A. S. Acute respiratory distress syndrome advances in diagnosis and treatment. *JAMA - Journal of the American Medical Association*, 319(7):698–710, 2018. ISSN 15383598. doi: 10.1001/jama.2017.21907.

Fernandez, A., Sturmberg, J., Lukersmith, S., Madden, R., Torkfar, G., Colagiuri, R., and Salvador-Carulla, L. Evidence-based medicine: Is it a bridge too far? *Health Research Policy and Systems*, 13(1):1–10, 2015. ISSN 14784505. doi: 10.1186/s12961-015-0057-0. URL http://dx.doi.org/10.1186/s12961-015-0057-0.

Flaatten, H. ARDS - Insights from Iceland and definitions from Berlin. *Acta Anaesthesiologica Scandinavica*, 57(1):1–2, 2013. ISSN 00015172. doi: 10.1111/aas.12021.

Freebairn, R. and Hickling, K. Spontaneous breathing during mechanical ventilation in ARDS. *Critical Care and Shock*, 8(3):61–66, 2005. ISSN 14107767.

Gammon, R. B., Shin, M. S., and Buchalter, S. E. Pulmonary barotrauma in mechanical ventilation; Patterns and risk factors. *Chest*, 102(2):568–572, 1992. ISSN 00123692. doi: 10.1378/chest.102.2.568. URL http://dx.doi.org/10.1378/chest.102.2.568.

Gappa, M., Stocks, J., Merkus, P., and Jobe, A. H. Lung growth and development after

preterm birth: Further evidence [3] (multiple letters). *American Journal of Respiratory and Critical Care Medicine*, 168(3):399–400, 2003. ISSN 1073449X. doi: 10.1164/ajrccm.168.3.955.

Gattinoni, L., Carlesso, E., Cadringher, P., Valenza, F., Vagginelli, F., and Chiumello, D. Physical and biological triggers of ventilator-induced lung injury and its prevention. *European Respiratory Journal*, 22(Supplement 47):15s–25s, 2003. ISSN 0903-1936. doi: 10.1183/09031936.03.00021303. URL http://erj.ersjournals.com/content/22/47{_}suppl/15s.short.

Georgopoulos, D., Prinianakis, G., and Kondili, E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Medicine*, 32(1):34–47, 2006. ISSN 03424642. doi: 10.1007/s00134-005-2828-5.

Gerstmann, D. R., Minton, S. D., Stoddard, R. A., Meredith, K. S., Monaco, F., Bertrand, J. M., Battisti, O., Langhendries, J. P., Francois, A., and Clark, R. H. The provo multicenter early high-frequency oscillatory ventilation trial: Improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics*, 98(6):1044–1057, 1996. ISSN 00314005.

Girard, T. D. and Bernard, G. R. Mechanical ventilation in ARDS: A state-of-the-art review. *Chest*, 131(3):921–929, 2007. ISSN 00123692. doi: 10.1378/chest.06-1515.

Goerke, J. Pulmonary surfactant: Functions and molecular composition. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, 1408(2-3):79–89, 1998. ISSN 09254439. doi: 10.1016/S0925-4439(98)00060-X. URL http://www.sciencedirect.com/science/article/pii/S092544399800060X.

Greenough, A. Late respiratory outcomes after preterm birth. *Early Human Development*, 83(12):785–788, 2007. ISSN 03783782. doi: 10.1016/j.earlhumdev.2007.09.006.

Greenspan, J., Abbasi, S., and Bhutani, V. Sequential changes in pulmonary mechanics in the very low birth weight ($\leq$ 1000 grams) infant. *The Journal of Pediatrics*, 113

(4):732–737, 1988. ISSN 00223476. doi: 10.1016/S0022-3476(88)80391-3. URL http://linkinghub.elsevier.com/retrieve/pii/S0022347688803913.

Griese, M. Pulmonary surfactant in health and human lung diseases: State of the art. *European Respiratory Journal*, 13(6):1455–1476, 1999. ISSN 09031936. doi: 10.1034/j.1399-3003.1999.13f36.x.

Grinnan, D. C. and Truwit, J. D. Clinical review: Respiratory mechanics in spontaneous and assisted ventilation. *Critical Care*, 9(5):472–484, 2005. ISSN 1364-8535. doi: 10.1186/cc3516. URL http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1297597/{%}5Cnhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC1297597/pdf/cc3516.pdf.

Group, H. S. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome. *The Journal of Pediatrics*, 122(4):609–619, apr 1993. ISSN 00223476. doi: 10.1016/S0022-3476(05)83548-6. URL https://linkinghub.elsevier.com/retrieve/pii/S0022347605835486.

Guerin, C. The preventive role of higher PEEP in treating severely hypoxemic ARDS. *Minerva Anestesiologica*, 77(8):835–845, 2011. ISSN 03759393.

Gutierrez, G., Ballarino, G. J., Turkan, H., Abril, J., De La Cruz, L., Edsall, C., George, B., Gutierrez, S., Jha, V., and Ahari, J. Automatic detection of patient-ventilator asynchrony by spectral analysis of airway flow. *Critical Care*, 15(4):R167, 2011. ISSN 13648535. doi: 10.1186/cc10309. URL http://ccforum.com/content/15/4/R167.

Halter, J. M., Steinberg, J. M., Schiller, H. J., DaSilva, M., Gatto, L. A., Landas, S., and Nieman, G. F. Positive end-expiratory pressure after a recruitment maneuver prevents both alveolar collapse and recruitment/derecruitment. *American Journal of Respiratory and Critical Care Medicine*, 167(12):1620–1626, 2003. ISSN 1073449X. doi: 10.1164/rccm.200205-435OC.

Hariton, E. and Locascio, J. J. Randomised controlled trials – the gold standard for ef-

fectiveness research: Study design: randomised controlled trials. *BJOG: An International Journal of Obstetrics and Gynaecology*, 125(13):1716, 2018. ISSN 14710528. doi: 10.1111/1471-0528.15199.

Hickling, K. G., Henderson, S. J., and Jackson, R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Medicine*, 16(6):372–377, sep 1990. ISSN 03424642. doi: 10.1007/BF01735174. URL http://link.springer.com/10.1007/BF01735174.

Hillman, K. and Albin, M. Pulmonary barotrauma during cardiopulmonary resuscitation. *Critical care medicine*, 14(7):606–9, jul 1986. ISSN 0090-3493. doi: 10.1097/00003246-198607000-00003. URL http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage{&}an=00003246-198607000-00003http://www.ncbi.nlm.nih.gov/pubmed/3720308.

Hislop, A. A., Wigglesworth, J. S., and Desai, R. Alveolar development in the human fetus and infant. *Early Human Development*, 13(1):1–11, feb 1986. ISSN 03783782. doi: 10.1016/0378-3782(86)90092-7. URL https://linkinghub.elsevier.com/retrieve/pii/0378378286900927.

Hjalmarson, O. and Sandberg, K. Abnormal lung function in healthy preterm infants. *American Journal of Respiratory and Critical Care Medicine*, 165(1):83–87, 2002. ISSN 1073449X. doi: 10.1164/ajrccm.165.1.2107093.

Hodgson, C. L., Tuxen, D. V., Davies, A. R., Bailey, M. J., Higgins, A. M., Holland, A. E., Keating, J. L., Pilcher, D. V., Westbrook, A. J., Cooper, D. J., and Nichol, A. D. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. *Critical care (London, England)*, 15(3):R133, 2011. ISSN 13648535. doi: 10.1186/cc10249. URL http://www.pubmedcentral.nih.gov/articlerender.

fcgi?artid=3219001{&}tool=pmcentrez{&}rendertype=abstracthttp://ccforum.com/content/15/3/R133.

Howe, S. L., Chase, J. G., Redmond, D. P., Morton, S. E., Kim, K. T., Pretty, C., Shaw, G. M., Tawhai, M. H., and Desaive, T. Inspiratory respiratory mechanics estimation by using expiratory data for reverse-triggered breathing cycles. *Computer Methods and Programs in Biomedicine*, 186:105184, 2020. ISSN 18727565. doi: 10.1016/j.cmpb.2019.105184. URL https://doi.org/10.1016/j.cmpb.2019.105184.

Jarreau, P. H., Louis, B., Dassieu, G., Desfrere, L., Blanchard, P. W., Moriette, G., Isabey, D., and Harf, A. Estimation of inspiratory pressure drop in neonatal and pediatric endotracheal tubes. *Journal of Applied Physiology*, 87(1):36–46, 1999. ISSN 8750-7587. URL http://www.ncbi.nlm.nih.gov/pubmed/10409556.

JM, D., Veness-Meehan, K., and Al., E. Changes in Pulmonary Mechanics After the Administration of Surfactant to Infants with Respiratory Distress Syndrome. *The New England journal of medicine*, 319:476, 1988.

Jobe, A. H. An unknown: Lung growth and development after very preterm birth. *American Journal of Respiratory and Critical Care Medicine*, 166(12 I):1529–1530, 2002. ISSN 1073449X. doi: 10.1164/rccm.2209012.

Jobe, A. H. Lung Recruitment for Ventilation: Does It Work, and is It Safe? *Journal of Pediatrics*, 154(5):635–636, 2009. ISSN 00223476. doi: 10.1016/j.jpeds.2009.01.059. URL http://dx.doi.org/10.1016/j.jpeds.2009.01.059.

Jobe, A. H. and Bancalari, E. Bronchopulmonary Dysplasia. *American Journal of Respiratory and Critical Care Medicine*, 163(7):1723–1729, jun 2001. ISSN 1073-449X. doi: 10.1164/ajrccm.163.7.2011060. URL http://www.atsjournals.org/doi/abs/10.1164/ajrccm.163.7.2011060.

Jobe, A. H. and Ikegami, M. Mechanisms initiating lung injury in the preterm. *Early*

Human Development, 53(1):81–94, 1998. ISSN 03783782. doi: 10.1016/S0378-3782(98)00045-0.

Joshi, S. and Kotecha, S. Lung growth and development. *Early Human Development*, 83 (12):789–794, 2007. ISSN 03783782. doi: 10.1016/j.earlhumdev.2007.09.007.

Kair, L. R., Leonard, D. T., and Anderson, J. D. M. Bronchopulmonary dysplasia. *Pediatrics in Review*, 33(6):255–263, 2012. ISSN 01919601. doi: 10.1542/pir.33-6-255.

Kannangara, D. O., Newberry, F., Howe, S., Major, V., Redmond, D., Szlavecs, A., Chiew, Y. S., Pretty, C., Benyo, B., Shaw, G. M., and Chase, J. G. Estimating the true respiratory mechanics during asynchronous pressure controlled ventilation. *Biomedical Signal Processing and Control*, 30:70–78, 2016a. ISSN 17468108. doi: 10.1016/j.bspc.2016.06.014. URL http://dx.doi.org/10.1016/j.bspc.2016.06.014.

Kannangara, D. O., Newberry, F., Howe, S., Major, V., Redmond, D., Szlavecz, A., Chiew, Y. S., Pretty, C., Benyo, B., Shaw, G. M., and Chase, J. G. Improved respiratory mechanical estimation during pressure controlled mechanical ventilation. In *IFMBE Proceedings*, 2016b. ISBN 9789811002656. doi: 10.1007/978-981-10-0266-3_29.

Kannangara, O., Dickson, J. L., and Chase, J. G. Specific compliance: is it truly independent of lung volume? *IFAC-PapersOnLine*, 51(27):299–304, 2018. ISSN 24058963. doi: 10.1016/j.ifacol.2018.11.625. URL https://linkinghub.elsevier.com/retrieve/pii/S2405896318333342.

Karanicolas, P. J., Farrokhyar, F., and Bhandari, M. Practical tips for surgical research: blinding: who, what, when, why, how? *Canadian journal of surgery. Journal canadien de chirurgie*, 53(5):345–8, oct 2010. ISSN 1488-2310. URL http://www.ncbi.nlm.nih.gov/pubmed/20858381http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2947122.

Kattwinkel, J., Niermeyer, S., Nadkarni, V., and Tibballs, J. ILCOR ADVISORY STATEMENT

: RESUSCITATION OF THE An Advisory Statement From the Pediatric Working Group of the. *Pediatrics*, 103(4):1–13, 1999. doi: 10.1542/peds.103.4.e56.

Keszler, M. INSURE, Infant Flow, Positive Pressure and Volume Guarantee - Tell us what is best: Selection of respiratory support modalities in the NICU. *Early Human Development*, 85(10 SUPPL.):S53—S56, 2009. ISSN 03783782. doi: 10.1016/j.earlhumdev.2009.08.016. URL http://dx.doi.org/10.1016/j.earlhumdev.2009.08.016.

Kim, K. T., Redmond, D. P., Morton, S. E., Howe, S. L., Chiew, Y. S., and Chase, J. G. Quantifying patient effort in spontaneously breathing patient using negative component of dynamic Elastance. *IFAC-PapersOnLine*, 50(1):5486–5491, 2017. ISSN 24058963. doi: 10.1016/j.ifacol.2017.08.1087.

Kim, K. T., Knopp, J., Dixon, B., and Chase, G. Quantifying neonatal pulmonary mechanics in mechanical ventilation. *Biomedical Signal Processing and Control*, 52:206–217, jul 2019a. ISSN 17468108. doi: 10.1016/j.bspc.2019.04.015. URL https://doi.org/10.1016/j.bspc.2019.04.015https://linkinghub.elsevier.com/retrieve/pii/S1746809419301120.

Kim, K. T., Knopp, J., Dixon, B., and Chase, J. G. Mechanically ventilated premature babies have sex differences in specific elastance: A pilot study. *Pediatric Pulmonology*, 55 (July):ppul.24538, oct 2019b. ISSN 8755-6863. doi: 10.1002/ppul.24538. URL https://onlinelibrary.wiley.com/doi/abs/10.1002/ppul.24538.

Kim, K. T., Morton, S., Howe, S., Chiew, Y. S., Knopp, J. L., Docherty, P., Pretty, C., Desaive, T., Benyo, B., Szlavecz, A., Moeller, K., Shaw, G. M., and Chase, J. G. Model-based PEEP titration versus standard practice in mechanical ventilation: a randomised controlled trial. *Trials*, 21(1):130, dec 2020. ISSN 1745-6215. doi: 10.1186/s13063-019-4035-7. URL https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-4035-7.

Kotecha, S. Lung growth: Implications for the newborn infant. *Archives of Disease in*

Childhood: Fetal and Neonatal Edition, 82(1):69–74, 2000. ISSN 14682052. doi: 10.1136/fn.82.1.F69.

Laghi, F. NAVA: Brain over machine? *Intensive Care Medicine*, 34(11):1966–1968, 2008. ISSN 03424642. doi: 10.1007/s00134-008-1215-4.

Lambermont, B., Ghuysen, A., Janssen, N., Morimont, P., Hartstein, G., Gerard, P., and D'Orio, V. Comparison of functional residual capacity and static compliance of the respiratory system during a positive end-expiratory pressure (PEEP) ramp procedure in an experimental model of acute respiratory distress syndrome. *Critical care (London, England)*, 12(4):R91, 2008. ISSN 1466-609X. doi: 10.1186/cc6961.

Langdon, R., Docherty, P. D., and Chase, J. G. Basis Function Modelling of Respiratory Patients with High or Low Auto-PEEP. *IFAC-PapersOnLine*, 50(1):15121–15126, 2017. ISSN 24058963. doi: 10.1016/j.ifacol.2017.08.2246. URL https://doi.org/10.1016/j.ifacol.2017.08.2246.

Langdon, R., Docherty, P. D., Chiew, Y. S., Möller, K., and Chase, J. G. Use of basis functions within a non-linear autoregressive model of pulmonary mechanics. *Biomedical Signal Processing and Control*, 27:44–50, 2016. ISSN 17468108. doi: 10.1016/j.bspc.2016.01.010. URL http://dx.doi.org/10.1016/j.bspc.2016.01.010.

Langston, C., Kida, K., Reed, M., and Thurlbeck, W. M. Human lung growth in late gestation and in the neonate. *American Review of Respiratory Disease*, 1984. ISSN 00030805.

Lauterbach, M. D., Raz, S., and Sander, C. J. Neonatal hypoxic risk in preterm birth infants: The influence of sex and severity of respiratory distress on cognitive recovery. *Neuropsychology*, 15(3):411–420, 2001. ISSN 08944105. doi: 10.1037/0894-4105.15.3.411.

Liggins, G. C., Howie, R. N., G. C. Liggins, Howie, R. N., Liggins, G. C., and Howie, R. N. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics*, 50(4):515–25, 1972. ISSN

0031-4005. doi: 10.1542/peds.102.1.S1.250. URL http://www.ncbi.nlm.nih.gov/pubmed/4561295.

Lipes, J., Bojmehrani, A., and Lellouche, F. Low tidal volume ventilation in patients without acute respiratory distress syndrome: A paradigm shift in mechanical ventilation. *Critical Care Research and Practice*, 2012, 2012. ISSN 20901305. doi: 10.1155/2012/416862.

Lista, G., Maturana, A., and Moya, F. R. Achieving and maintaining lung volume in the preterm infant: from the first breath to the NICU. *European Journal of Pediatrics*, 176 (10):1287–1293, 2017. ISSN 14321076. doi: 10.1007/s00431-017-2984-y.

Luks, A. M. Ventilatory strategies and supportive care in acute respiratory distress syndrome. *Influenza and other Respiratory Viruses*, 7(SUPPL.3):8–17, 2013. ISSN 17502640. doi: 10.1111/irv.12178.

MacIntyre, N. R. Respiratory function during pressure support ventilation. *Chest*, 89(5): 677–683, 1986. ISSN 00123692. doi: 10.1378/chest.89.5.677.

Major, V., Corbett, S., Redmond, D., Beatson, A., Glassenbury, D., Chiew, Y. S., Pretty, C., Desaive, T., Szlávecz, Á., Benyó, B., Shaw, G. M., and Chase, J. G. Respiratory mechanics assessment for reverse-triggered breathing cycles using pressure reconstruction. *Biomedical Signal Processing and Control*, 23:1–9, 2016a. ISSN 17468108. doi: 10.1016/j.bspc.2015.07.007. URL http://dx.doi.org/10.1016/j.bspc.2015.07.007.

Major, V., Corbett, S., Redmond, D., Beatson, A., Glassenbury, D., Chiew, Y. S., Pretty, C., Desaive, T., Szlávecz, Á., Benyó, B., Shaw, G. M., and Chase, J. G. Respiratory mechanics assessment for reverse-triggered breathing cycles using pressure reconstruction. *Biomedical Signal Processing and Control*, 23:1–9, 2016b. ISSN 17468108. doi: 10.1016/j.bspc.2015.07.007. URL http://dx.doi.org/10.1016/j.bspc.2015.07.007.

Major, V. J., Chiew, Y. S., Shaw, G. M., and Chase, J. G. Biomedical engineer's guide to

the clinical aspects of intensive care mechanical ventilation. *BioMedical Engineering Online*, 17(1), 2018. ISSN 1475925X. doi: 10.1186/s12938-018-0599-9.

Major, V. J. Randomisde Controlled Trial Initialistation and Management in the Intensive Care Unit. Master's thesis, Mechanical Engineering, University of Canterbury, 2015.

Malbouisson, L. M., Muller, J. C., Constantin, J. M., Lu, Q., Puybasset, L., Rouby, J. J., and Group, C. T. S. A. S. Computed tomography assessment of positive end-expiratory pressure-induced alveolar recruitment in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*, 163(6):1444–1450, 2001. URL http://www.ncbi.nlm.nih.gov/pubmed/11371416.

Meade, M. O., Cook, D. J., Guyatt, G. H., Slutsky, A. S., Arabi, Y. M., Cooper, D. J., Davies, A. R., Hand, L. E., Zhou, Q., Thabane, L., Austin, P., Lapinsky, S., Baxter, A., Russell, J., Skrobik, Y., Ronco, J. J., Stewart, T. E., Guyatt, G. H., Slutsky, A. S., Arabi, Y. M., Cooper, D. J., Davies, A. R., Hand, L. E., Zhou, Q., Thabane, L., Austin, P., Lapinsky, S., Baxter, A., Russell, J., Skrobik, Y., Ronco, J. J., and Stewart, T. E. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. *JAMA - Journal of the American Medical Association*, 299(6):637–645, 2008. ISSN 00987484. doi: 10.1001/jama.299.6.637.

Mellott, K. G., Grap, M. J., Munro, C. L., Sessler, C. N., Wetzel, P. A., Nilsestuen, J. O., and Ketchum, J. M. Patient ventilator asynchrony in critically ill adults: Frequency and types. *Heart and Lung: Journal of Acute and Critical Care*, 43(3):231–243, 2014. ISSN 15273288. doi: 10.1016/j.hrtlng.2014.02.002. URL http://dx.doi.org/10.1016/j.hrtlng.2014.02.002.

Mercat, A., Richard, J.-C. M., Vielle, B., Jaber, S., Osman, D., Diehl, J.-L., Lefrant, J.-Y., Prat, G., Richecoeur, J., Nieszkowska, A., Gervais, C., Baudot, J., Bouadma, L., Brochard, L., and for the Expiratory Pressure (Express) Study Group. Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress

Syndrome. *JAMA*, 299(6):646, feb 2008a. ISSN 0098-7484. doi: 10.1001/jama.299.6.646. URL http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.299.6.646.

Mercat, A., Richard, J.-c. M., Vielle, B., Jaber, S., Osman, D., Diehl, J.-L., Lefrant, J.-Y., Prat, G., Richecoeur, J., Nieszkowska, A., Gervais, C., Baudot, J., Bouadma, L., Brochard, L., and Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*, 299(6):646–55, feb 2008b. ISSN 1538-3598. doi: 10.1001/jama.299.6.646. URL http://www.ncbi.nlm.nih.gov/pubmed/18270353.

Mertens, M., Tabuchi, A., Meissner, S., Krueger, A., Schirrmann, K., Kertzscher, U., Pries, A. R., Slutsky, A. S., Koch, E., and Kuebler, W. M. Alveolar dynamics in acute lung injury: heterogeneous distension rather than cyclic opening and collapse. *Critical care medicine*, 37(9):2604–2611, 2009. ISSN 0090-3493. doi: 10.1097/CCM.0b013e3181a5544d.

Miller, H. C. and Futrakul, P. Birth weight, gestational age, and sex as determining factors in the incidence of respiratory distress syndrome of prematurely born infants. *The Journal of pediatrics*, 72(5):628–635, 1968. ISSN 0022-3476. URL http://ovidsp.ovid.com/ovidweb.cgi?T=JS{&}PAGE=reference{&}D=med1{&}NEWS=N{&}AN=5646363.

Möller, K., Kretschmer, J., and Schranz, C. Hierarchical Modeling for Medical Decision Support. *2011 4th International Conference on Biomedical Engineering and Informatics (BMEI)*, 2:960–964, 2011.

Moorhead, K. T., Piquilloud, L., Lambermont, B., Roeseler, J., Chiew, Y. S., Chase, J. G., Revelly, J. P., Bialais, E., Tassaux, D., Laterre, P. F., Jolliet, P., Sottiaux, T., and Desaive, T. NAVA enhances tidal volume and diaphragmatic electro-myographic activity matching: A Range90 analysis of supply and demand. *Journal of Clinical Monitoring and Computing*, 27(1):61–70, 2013. ISSN 13871307. doi: 10.1007/s10877-012-9398-1.

Morton, S. E., Dickson, J., Chase, J. G., Docherty, P., Desaive, T., Howe, S. L., Shaw, G. M.,

and Tawhai, M. A virtual patient model for mechanical ventilation. *Computer Methods and Programs in Biomedicine*, 165:77–87, 2018. ISSN 18727565. doi: 10.1016/j.cmpb.2018.08.004. URL https://doi.org/10.1016/j.cmpb.2018.08.004.

Morton, S., Chiew, Y., Pretty, C., Moltchanova, E., Scarrott, C., Redmond, D., Shaw, G., and Chase, J. Effective sample size estimation for a mechanical ventilation trial through Monte-Carlo simulation: Length of mechanical ventilation and Ventilator Free Days. *Mathematical Biosciences*, 284:21–31, feb 2017. ISSN 00255564. doi: 10.1016/j.mbs.2016.06.001. URL https://linkinghub.elsevier.com/retrieve/pii/S0025556416300621.

Morton, S. E., Knopp, J. L., Chase, J. G., Docherty, P., Howe, S. L., Möller, K., Shaw, G. M., and Tawhai, M. Optimising mechanical ventilation through model-based methods and automation. *Annual Reviews in Control*, 48:369–382, 2019a. ISSN 13675788. doi: 10.1016/j.arcontrol.2019.05.001. URL https://doi.org/10.1016/j.arcontrol.2019.05.001.

Morton, S. E., Knopp, J. L., Chase, J. G., Möller, K., Docherty, P., Shaw, G. M., and Tawhai, M. Predictive Virtual Patient Modelling of Mechanical Ventilation: Impact of Recruitment Function. *Annals of Biomedical Engineering*, 47(7):1626–1641, jul 2019b. ISSN 0090-6964. doi: 10.1007/s10439-019-02253-w. URL http://link.springer.com/10.1007/s10439-019-02253-w.

Motulsky, H. *Intuitive Biostatistics.* Oxford University Press, New York, 1995. ISBN 0-19-508606-6.-ISBN 0-19-508607-a.

Motulsky, H. J. Common misconceptions about data analysis and statistics. *British Journal of Pharmacology*, 172(8):2126–2132, apr 2015. ISSN 00071188. doi: 10.1111/bph.12884. URL http://doi.wiley.com/10.1111/bph.12884.

Mulqueeny, Q., Ceriana, P., Carlucci, A., Fanfulla, F., Delmastro, M., and Nava, S. Automatic detection of ineffective triggering and double triggering during mechanical

ventilation. *Intensive Care Medicine*, 33(11):2014–2018, 2007. ISSN 03424642. doi: 10.1007/s00134-007-0767-z.

Neto, A. S., Nagtzaam, L., and Schultz, M. J. Ventilation with lower tidal volumes for critically ill patients without the acute respiratory distress syndrome: A systematic translational review and meta-Analysis. *Current Opinion in Critical Care*, 20(1):25–32, 2014. ISSN 10705295. doi: 10.1097/MCC.0000000000000044.

Neumann, R. P. and Von Ungern-Sternberg, B. S. The neonatal lung - Physiology and ventilation. *Paediatric Anaesthesia*, 24(1):10–21, 2014. ISSN 11555645. doi: 10.1111/pan.12280.

Newberry, F., Kannangara, O., Howe, S., Major, V., Redmond, D., Szlavecz, A., Chiew, Y. S., Pretty, C., Benyo, B., Shaw, G. M., and Chase, J. G. Iterative interpolative pressure reconstruction for improved respiratory mechanics estimation during asynchronous volume controlled ventilation. In *IFMBE Proceedings*, volume 56, pages 133–139, 2016. ISBN 9789811002656. doi: 10.1007/978-981-10-0266-3_27.

Niermeyer, S., Kattwinkel, J., Van Reempts, P., Nadkarni, V., Phillips, B., Zideman, D., Azzopardi, D., Berg, R., Boyle, D., Boyle, R., Burchfield, D., Carlo, W., Chameides, L., Denson, S., Fallat, M., Gerardi, M., Gunn, A., Hazinski, M. F., Keenan, W., Knaebel, S., Milner, A., Perlman, J., Saugstad, O. D., Schleien, C., Solimano, A., Speer, M., Toce, S., Wiswell, T., and Zaritsky, A. International Guidelines for Neonatal Resuscitation: An excerpt from the Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care: International Consensus on Science. Contributors and Reviewers for the Neonatal Resuscitation Gui. *Pediatrics*, 106(3), 2000. ISSN 10984275. doi: 10.1542/peds.106.3.e29.

Oba, Y., Thameem, D. M., and Zaza, T. High levels of PEEP may improve survival in acute respiratory distress syndrome: A meta-analysis. *Respiratory Medicine*, 103(8):1174–1181, 2009. ISSN 09546111. doi: 10.1016/j.rmed.2009.02.008. URL `http://dx.doi.org/10.1016/j.rmed.2009.02.008`.

Oczenski, W., Hörmann, C., Keller, C., Lorenzl, N., Kepka, A., Schwarz, S., and Fitzgerald, R. D. Recruitment maneuvers after a positive end-expiratory pressure trial do not induce sustained effects in early adult respiratory distress syndrome. *Anesthesiology*, 101(3):620–625, 2004. ISSN 0003-3022. doi: 10.1097/00000542-200409000-00010.

O'Donnell, C. P., Davis, P. G., and Morley, C. J. Positive pressure ventilation at neonatal resuscitation: Review of equipment and international survey of practice. *Acta Paediatrica, International Journal of Paediatrics*, 93(5):583–588, 2004. ISSN 08035253. doi: 10.1080/08035250410026581.

Oliva, P. D. L., Schüffelmann, C., Ana, G. Z., Villar, J., and Kacmarek, R. M. Asynchrony, neural drive, ventilatory variability and COMFORT: NAVA versus pressure support in pediatric patients. A non-randomized cross-over trial. *Intensive Care Medicine*, 38(5): 838–846, 2012. ISSN 03424642. doi: 10.1007/s00134-012-2535-y.

Pannu, N. and Mehta, R. L. Effect of mechanical ventilation on the kidney. *Best Practice and Research: Clinical Anaesthesiology*, 18(1):189–203, 2004. ISSN 15216896. doi: 10.1016/j.bpa.2003.08.002.

Parker, J. C., Hernandez, L. A., and Peevy, K. J. Mechanisms of ventilator-induced lung injury, 1993. ISSN 00903493.

Patel, S. B. and Kress, J. P. Sedation and analgesia in the mechanically ventilated patient. *American Journal of Respiratory and Critical Care Medicine*, 185(5):486–497, 2012. ISSN 1073449X. doi: 10.1164/rccm.201102-0273CI.

Peacock, J. L., Marston, L., Marlow, N., Calvert, S. A., and Greenough, A. Neonatal and infant outcome in boys and girls born very prematurely. *Pediatric Research*, 71(3): 305–310, 2012. ISSN 00313998. doi: 10.1038/pr.2011.50.

Pelosi, P., Goldner, M., Mckibben, A., Adams, A., Eccher, G., Caironi, P., Losappio, S., Gattinoni, L., and Marini, J. J. Recruitment and Derecruitment During Acute An Experimental Study. 164:122–130, 2001.

Pelosi, P., de Abreu, M. G., and Rocco, P. R. M. New and conventional strategies for lung recruitment in acute respiratory distress syndrome. *Critical Care*, 14(2), 2010. ISSN 13648535. doi: 10.1186/cc8851.

Petersen, G. W. and Baier, H. Incidence of pulmonary barotrauma in a medical ICU. *Critical care medicine*, 11(2):67–9, feb 1983. ISSN 0090-3493. doi: 10.1097/00003246-198302000-00002. URL http://journals.lww.com/00003246-198302000-00002http://www.ncbi.nlm.nih.gov/pubmed/6337021.

Phelan, P. D. and Williams, H. E. Ventilatory Studies in Healthy Infants. *Pediatr Res*, 3(5):425–432, 1969. ISSN 0031-3998. URL http://dx.doi.org/10.1203/00006450-196909000-00005.

Phua, J., Badia, J. R., Adhikari, N. K., Friedrich, J. O., Fowler, R. A., Singh, J. M., Scales, D. C., Stather, D. R., Li, A., Jones, A., Gattas, D. J., Hallett, D., Tomlinson, G., Stewart, T. E., and Ferguson, N. D. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. *American Journal of Respiratory and Critical Care Medicine*, 179(3):220–227, 2009. ISSN 1073449X. doi: 10.1164/rccm.200805-722OC.

Pintado, M.-C., de Pablo, R., Trascasa, M., Milicua, J.-M., Rogero, S., Daguerre, M., Cambronero, J.-A., Arribas, I., and Sánchez-García, M. Individualized PEEP setting in subjects with ARDS: a randomized controlled pilot study. *Respiratory care*, 58(9):1416–23, 2013. ISSN 1943-3654. doi: 10.4187/respcare.02068. URL http://www.ncbi.nlm.nih.gov/pubmed/23362167.

Piquilloud, L., Vignaux, L., Bialais, E., Roeseler, J., Sottiaux, T., Laterre, P. F., Jolliet, P., and Tassaux, D. Neurally adjusted ventilatory assist improves patient-ventilator interaction. *Intensive Care Medicine*, 37(2):263–271, 2011. ISSN 03424642. doi: 10.1007/s00134-010-2052-9.

Plavka, R., Kopecký, P., Sebroň, V., Svihovec, P., Zlatohlávková, B., and Januš, V. A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respi-

ratory distress syndrome. *Intensive Care Medicine*, 25(1):68–75, 1999. ISSN 03424642. doi: 10.1007/s001340050789.

Polin, R. A., Carlo, W. A., Papile, L. A., Tan, R., Kumar, P., Benitz, W., Eichenwald, E., Cummings, J., and Baley, J. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics*, 133(1):156–163, 2014. ISSN 00314005. doi: 10.1542/peds.2013-3443.

Poole, S. F., Chiew, Y. S., Redmond, D. P., Davidson, S. M., Damanhuri, N. S., Pretty, C., Docherty, P. D., Desaive, T., Shaw, G. M., and Chase, J. G. Real-time breath-to-breath asynchrony event detection using time-varying respiratory elastance model. In *IFAC Proceedings Volumes (IFAC-PapersOnline)*, 2014. ISBN 9783902823625.

Putensen, C., Hering, R., and Wrigge, H. Spontaneous Breathing During Ventilatory Support in Patients with ARDS. *Mechanical Ventilation*, 2005. URL http://link.springer.com/chapter/10.1007/3-540-26791-3{_}24.

Raghavendran, K. and Napolitano, L. M. Definition of ALI/ARDS. *Critical Care Clinics*, 27(3):429–437, jul 2011. ISSN 07490704. doi: 10.1016/j.ccc.2011.05.006. URL https://linkinghub.elsevier.com/retrieve/pii/S0749070411000273.

Ranieri, V. M., Rubenfeld, G. D., Thompson, B. T., Ferguson, N. D., Caldwell, E., Fan, E., Camporota, L., and Slutsky, A. S. Acute respiratory distress syndrome: The Berlin definition. *JAMA - Journal of the American Medical Association*, 307(23):2526–2533, 2012. ISSN 00987484. doi: 10.1001/jama.2012.5669.

Redmond, D., Chiew, Y. S., Van Drunen, E., Shaw, G. M., and Chase, J. G. A minimal algorithm for a minimal recruitment model-model estimation of alveoli opening pressure of an acute respiratory distress syndrome (ARDS) lung. *Biomedical Signal Processing and Control*, 14(1):1–8, 2014. ISSN 17468108. doi: 10.1016/j.bspc.2014.05.006. URL http://dx.doi.org/10.1016/j.bspc.2014.05.006.

Redmond, D. P., Chiew, Y. S., Major, V., and Chase, J. G. Evaluation of model-based meth-

ods in estimating respiratory mechanics in the presence of variable patient effort. *Computer Methods and Programs in Biomedicine*, 171:67–79, 2019. ISSN 18727565. doi: 10.1016/j.cmpb.2016.09.011.

Rettwitz-Volk, W., Veldman, A., Roth, B., Vierzig, A., Kachel, W., Varnholt, V., Schlosser, R., and Von Loewenich, V. A prospective, randomized, multicenter trial of high frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. *Journal of Pediatrics*, 132(2):249–254, 1998. ISSN 00223476. doi: 10.1016/S0022-3476(98)70440-8.

Riva, D., Contador, R., Baez-Garcia, C., Xisto, D., Cagido, V., Martini, S., Morales, M., Rocco, P., Faffe, D., and Zin, W. Recruitment maneuver: RAMP versus CPAP pressure profile in a model of acute lung injury. *Respiratory Physiology & Neurobiology*, 169(1):62–68, oct 2009. ISSN 15699048. doi: 10.1016/j.resp.2009.08.010. URL https://linkinghub.elsevier.com/retrieve/pii/S1569904809002468.

Rose, L., Presneil, J. J., Johnston, L., Nelson, S., Cade, J. F., Care, I., Health, P., and Complete, M. Ventilation and weaning practices in Australia and New Zealand. *Anaesthesia and Intensive Care*, 37(1):99–107, 2009. ISSN 0310057X. doi: 10.1016/j.aucc.2007.12.003.

Rose, L. Clinical application of ventilator modes: Ventilatory strategies for lung protection. *Australian Critical Care*, 23(2):71–80, 2010. ISSN 10367314. doi: 10.1016/j.aucc.2010.03.003. URL http://dx.doi.org/10.1016/j.aucc.2010.03.003.

Rubenfeld, G. D., Caldwell, E., Peabody, E., Weaver, J., Martin, D. P., Neff, M., Stern, E. J., and Hudson, L. D. Incidence and outcomes of acute lung injury. *The New England journal of medicine*, 353(16):1685–93, oct 2005. ISSN 1533-4406. doi: 10.1056/NEJMoa050333. URL http://www.ncbi.nlm.nih.gov/pubmed/16236739.

Schranz, C., Becher, T., Schädler, D., Weiler, N., and Möller, K. Model-Based Ventilator Settings in Pressure Controlled Ventilation. *Biomedical Engineering/Biomedizinische Technik*, c(6):10–11, 2013. doi: 10.1515/bmt-2013-4.

Schranz, C., Docherty, P. D., Chiew, Y., Möller, K., and Chase, J. Iterative integral parameter identification of a respiratory mechanics model. *BioMedical Engineering OnLine*, 11:38, 2012a. ISSN 1475-925X. doi: 10.1186/1475-925X-11-38.

Schranz, C., Docherty, P. D., Chiew, Y. S., Chase, J. G., and Möller, K. Structural identifiability and practical applicability of an alveolar recruitment model for ARDS patients. *IEEE Transactions on Biomedical Engineering*, 59(12):3396–3404, 2012b. ISSN 00189294. doi: 10.1109/TBME.2012.2216526.

Schranz, C., Docherty, P. D., Chiew, Y. S., Chase, J. G., and Möller, K. Structural identifiability and practical applicability of an alveolar recruitment model for ards patients. *IEEE Transactions on biomedical engineering*, 59(12):3396–3404, 2012c.

Sibbald, B. and Roland, M. Why are randomised controlled trials important? *British Medical Journal*, 316(7126):201, 1998. ISSN 09598146.

Sigurdsson, M. I., Sigvaldason, K., Gunnarsson, T. S., Moller, A., and Sigurdsson, G. H. Acute respiratory distress syndrome: Nationwide changes in incidence, treatment and mortality over 23 years. *Acta Anaesthesiologica Scandinavica*, 57(1):37–45, 2013. ISSN 00015172. doi: 10.1111/aas.12001.

Sinderby, C., Spahija, J., and Beck, J. Neurally-adjusted Ventilatory Assist. In *Mechanical Ventilation*, volume 21, pages 125–134. Springer-Verlag, Berlin/Heidelberg, 2015. ISBN 978-3-540-26791-1. doi: 10.1007/3-540-26791-3_9. URL `http://link.springer.com/10.1007/3-540-26791-3{_}9`.

Sinderby, C., Beck, J., Spahija, J., De Marchie, M., Lacroix, J., Navalesi, P., and Slutsky, A. S. Inspiratory muscle unloading by neurally adjucted ventilatory assist during maximal inspiratory efforts in healthy subjects. *Chest*, 131(3):711–717, 2007. ISSN 00123692. doi: 10.1378/chest.06-1909.

Slutsky, A. S. Lung Injury Caused by Mechanical Ventilation. *Chest*, 116:9S–15S, jul 1999. ISSN 00123692. doi: 10.1378/chest.116.suppl_1.9S-a. URL `http:`

//www.sciencedirect.com/science/article/pii/S0012369215306395https://linkinghub.elsevier.com/retrieve/pii/S0012369215306395.

Slutsky, A. S. and Ranieri, V. M. Ventilator-induced lung injury. *New England Journal of Medicine*, 369(22):2126–2136, 2013a. ISSN 15334406. doi: 10.1056/NEJMra1208707.

Slutsky, A. S. and Ranieri, V. M. Ventilator-induced lung injury. *New England Journal of Medicine*, 369(22):2126–2136, 2013b. ISSN 15334406. doi: 10.1056/NEJMra1208707.

Spahija, J., de Marchie, M., Albert, M., Bellemare, P., Delisle, S., Beck, J., and Sinderby, C. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Critical care medicine*, 38(2):518–526, 2010. ISSN 0090-3493. doi: 10.1097/CCM.0b013e3181cb0d7b.

Stevenson, D. K., Verter, J., Fanaroff, A. A., Oh, W., Ehrenkranz, R. A., Shankaran, S., Donovan, E. F., Wright, L. L., Lemons, J. A., Tyson, J. E., Korones, S. B., Bauer, C. R., Stoll, B. J., Papile, L. A., Verter, J., Fanaroff, A. A., Oh, W., Ehrenkranz, R. A., Shankaran, S., Donovan, E. F., Wright, L. L., and Lemons, J. A. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. *Archives of disease in childhood. Fetal and neonatal edition*, 83(3):F182–5, 2000. ISSN 1359-2998. doi: 10.1136/Fn.83.3.F182. URL http://www.ncbi.nlm.nih.gov/pubmed/11040165{%}5Cnhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1721180http://fn.bmj.com/cgi/doi/10.1136/fn.83.3.F182.

Stocks, J., Coates, A., and Bush, A. Lung function in infants and young children with chronic lung disease of infancy: The next steps? *Pediatric Pulmonology*, 42(1):3–9, 2007. ISSN 87556863. doi: 10.1002/ppul.20520.

Suarez-Sipmann, F., Böhm, S. H., Tusman, G., Pesch, T., Thamm, O., Reissmann, H., Reske, A., Magnusson, A., and Hedenstierna, G. Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. *Critical care medicine*, 35(1):214–21, 2007. ISSN 0090-3493. doi: 10.1097/01.CCM.0000251131.40301.E2. URL http://www.ncbi.nlm.nih.gov/pubmed/17110872.

Sundaresan, A. and Chase, J. G. Positive end expiratory pressure in patients with acute respiratory distress syndrome - The past, present and future. *Biomedical Signal Processing and Control*, 7(2):93–103, 2012. ISSN 17468094. doi: 10.1016/j.bspc.2011.03.001. URL http://dx.doi.org/10.1016/j.bspc.2011.03.001.

Sundaresan, A., Yuta, T., Hann, C. E., Geoffrey Chase, J., Shaw, G. M., Chase, J. G., and Shaw, G. M. A minimal model of lung mechanics and model-based markers for optimizing ventilator treatment in ARDS patients. *Computer Methods and Programs in Biomedicine*, 95(2):166–180, 2009. ISSN 01692607. doi: 10.1016/j.cmpb.2009.02.008.

Sundaresan, A., Chase, J. G., Shaw, G. M., Chiew, Y. S., and Desaive, T. Model-based optimal PEEP in mechanically ventilated ARDS patients in the intensive care unit. *Biomedical engineering online*, 10(1):64, 2011. ISSN 1475-925X. doi: 10.1186/1475-925X-10-64. URL http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3167768{&}tool=pmcentrez{&}rendertype=abstract.

Suter, P. M., Fairley, H. B., and Isenberg, M. D. Optimum End-Expiratory Airway Pressure in Patients with Acute Pulmonary Failure. *New England Journal of Medicine*, 292(6):284–289, feb 1975. ISSN 0028-4793. doi: 10.1056/NEJM197502062920604. URL http://www.nejm.org/doi/abs/10.1056/NEJM197502062920604.

Sweet, D. G., Carnielli, V., Greisen, G., Hallman, M., Ozek, E., Plavka, R., Saugstad, O. D., Simeoni, U., Speer, C. P., and Halliday, H. L. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 update. In *Neonatology*, volume 97, pages 402–417, 2010. ISBN 1661-7800. doi: 10.1159/000297773.

Sweet, D. G., Carnielli, V., Greisen, G., Hallman, M., Ozek, E., Plavka, R., Saugstad, O. D., Simeoni, U., Speer, C. P., Vento, M., and Halliday, H. L. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants-2013 update. *Neonatology*, 103(4):353–368, 2013. ISSN 16617800. doi: 10.1159/000349928.

Szlavecz, A., Chiew, Y. S., Redmond, D., Beatson, A., Glassenbury, D., Corbett, S., Major, V., Pretty, C., Shaw, G. M., Benyo, B., Desaive, T., and Chase, J. G. The Clinical Utilisation of Respiratory Elastance Software (CURE Soft): a bedside software for real-time respiratory mechanics monitoring and mechanical ventilation management. *Biomedical engineering online*, 13(1):140, 2014. ISSN 1475-925X. doi: 10.1186/1475-925X-13-140. URL http://www.biomedical-engineering-online.com/content/13/1/140.

Tejeda, M., Boix, J. H., Álvarez, F., Balanzá, R., and Morales, M. Comparison of pressure support ventilation and assist-control ventilation in the treatment of respiratory failure. *Chest*, 111(5):1322–1325, 1997. ISSN 00123692. doi: 10.1378/chest.111.5.1322.

Thammanomai, A., Hamakawa, H., Bartolák-Suki, E., and Suki, B. Combined Effects of Ventilation Mode and Positive End-Expiratory Pressure on Mechanics, Gas Exchange and the Epithelium in Mice with Acute Lung Injury. *PLoS ONE*, 8(1):1–10, 2013. ISSN 19326203. doi: 10.1371/journal.pone.0053934.

Thille, A. W., Rodriguez, P., Cabello, B., Lellouche, F., and Brochard, L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Medicine*, 32(10): 1515–1522, 2006. ISSN 03424642. doi: 10.1007/s00134-006-0301-8.

Thille, A. W., Cabello, B., Galia, F., Lyazidi, A., and Brochard, L. Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. *Intensive Care Medicine*, 34(8):1477–1486, 2008. ISSN 03424642. doi: 10.1007/s00134-008-1121-9.

Thomas, P. a. A Comparative Study of Lung Compliance and Pulmonary Surfactant Activity in Human Subjects. *The Annals of Thoracic Surgery*, 11(2):133–139, 1971. ISSN 00034975. doi: 10.1016/S0003-4975(10)65427-6.

Todd, S., Whitehead, A., Stallard, N., and Whitehead, J. Interim analyses and sequential designs in phase III studies. *British Journal of Clinical Pharmacology*, 51(5):394–399, 2001. ISSN 03065251. doi: 10.1046/j.1365-2125.2001.01382.x.

Torday, J. S. and Nielsen, H. C. The sex difference in fetal lung surfactant production. *Experimental Lung Research*, 12(1):1–19, 1987. ISSN 01902148. doi: 10.3109/01902148709068811.

Torday, J. S., Nielsen, H. C., Fencl, M. d. M., Avery, M. E., Fencl Mde, M., and Avery, M. E. Sex differences in fetal lung maturation. *The American review of respiratory disease*, 123(2):205–208, feb 1981. ISSN 0003-0805. doi: 10.1164/arrd.1981.123.2.205. URL http://www.ncbi.nlm.nih.gov/pubmed/6894519.

Tremblay, L. N. and Slutsky, A. S. Ventilator-induced lung injury: from the bench to the bedside. In *Applied Physiology in Intensive Care Medicine*, number January, pages 357–366. Springer Berlin Heidelberg, Berlin, Heidelberg, 2006. ISBN 3540373616. doi: 10.1007/3-540-37363-2_50. URL http://link.springer.com/10.1007/3-540-37363-2{_}50.

Van Reempts, P., Borstlap, C., Laroche, S., and Van der Auwera, J. C. Early use of high frequency ventilation in the premature neonate. *European Journal of Pediatrics*, 162 (4):219–226, 2003. ISSN 03406199. doi: 10.1007/s00431-002-1145-z.

Vicario, F., Albanese, A., Karamolegkos, N., Wang, D., Seiver, A., and Chbat, N. W. Noninvasive estimation of respiratory mechanics in spontaneously breathing ventilated patients: A constrained optimization approach. *IEEE Transactions on Biomedical Engineering*, 63(4):775–787, 2016. ISSN 15582531. doi: 10.1109/TBME.2015.2470641.

Villar, J., Kacmarek, R. M., Perez-Mendez, L., and Aguirre-Jaime, A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Critical care medicine*, 34(5):1311–1318, 2006. ISSN 0090-3493 (Print). doi: 10.1097/01.CCM.0000215598.84885.01.

Villar, J., Pérez-Méndez, L., Blanco, J., Añón, J. M., Blanch, L., Belda, J., Santos-Bouza, A., Fernández, R. L., Kacmarek, R. M., Spanish Initiative for Epidemiology, S., and Therapies for, A. N. A universal definition of ARDS: The PaO2/FiO2 ratio under a stan-

dard ventilatory setting - A prospective, multicenter validation study. *Intensive Care Medicine*, 39(4):583–592, 2013. ISSN 03424642. doi: 10.1007/s00134-012-2803-x.

West, J. B. *Respiratory physiology: The essentials*, volume 69. LWW; Ninth edition (September 21, 2011), jan 1975. ISBN 9781609136406. doi: 10.1016/0007-0971(75)90100-X. URL https://linkinghub.elsevier.com/retrieve/pii/000709717590100X.

Wøien, H., Stubhaug, A., and Bjørk, I. T. Analgesia and sedation of mechanically ventilated patients A national survey of clinical practice. *Acta Anaesthesiologica Scandinavica*, 56(1):23–29, 2012. ISSN 00015172. doi: 10.1111/j.1399-6576.2011.02524.x.

Wood, A. J. and Jobe, A. H. Pulmonary Surfactant Therapy. *New England Journal of Medicine*, 328(12):861–868, mar 1993. ISSN 0028-4793. doi: 10.1056/NEJM199303253281208. URL http://www.nejm.org/doi/abs/10.1056/NEJM199303253281208.

Yoder, B. A., Siler-Khodr, T., Winter, V. T., and Coalson, J. J. High-frequency oscillatory ventilation: Effects on lung function, mechanics, and airway cytokines in the immature baboon model for neonatal chronic lung disease. *American Journal of Respiratory and Critical Care Medicine*, 162(5):1867–1876, 2000. ISSN 1073449X. doi: 10.1164/ajrccm.162.5.9912145.

Yuksel, B., Greenough, A., and Gamsu, H. R. Respiratory function at follow-up after neonatal surfactant replacement therapy. *Respiratory Medicine*, 87(3):217–221, 1993. ISSN 09546111. doi: 10.1016/0954-6111(93)90095-H.

Zarin, D. A., Tse, T., Williams, R. J., Califf, R. M., and Ide, N. C. The ClinicalTrials.gov results database - Update and key issues. *New England Journal of Medicine*, 364(9):852–860, 2011. ISSN 15334406. doi: 10.1056/NEJMsa1012065.